PROCEEDINGS

ST VINCENT'S CLINIC, SYDNEY

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ST VINCENT'S CLINIC
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EDITORIAL

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Editor, Proceedings

In this year of the death of Sr Bernice Elphick, I felt it was fitting in this twentieth issue of *Proceedings* to provide a brief history of St Vincent's Clinic, now in its nineteenth year of operation.

The concept of a Clinic originally commenced in the mid 1980s. At that time, there was a certain amount of political unrest in medical circles. A small group of doctors associated with St Vincent's Hospital met to consider the possibility of commencing a new clinic similar to some of the clinics in North America. The success of St Vincent's Private Hospital, then only 10 years old, was a great example of what could be done with ingenuity, vision and good management. The pioneering group comprised Drs John Roarty, Derek Berg, Thomas Hugh, Bruce Taylor, the late David Wilson and Professor James Biggs. The group felt that, with the cooperation of the Private Hospital, such a new venture could be realised. It would aim to be a multi-disciplinary clinic of excellence with different specialty groups working closely together both internally and externally for greater patient benefit. It aimed to provide radiotherapy and all forms of investigative procedures. It would be a further forum for education. It was vital to the concept of the Clinic that a research foundation be created.

This concept was presented to Sr Bernice who, as usual, perused the documentation very carefully before strongly endorsing the project and including a day surgery unit. At that time she informed the medical group that the Private Hospital had just acquired an adjacent property, an old hardware store on the corner of Oxford St, on which it was planned to expand the medical imaging department with the installation of a new computerised scanner. A small sub-committee was established, consisting of Sr Bernice, the aforementioned representatives of the doctors under the chairmanship of Dr John Roarty and representatives of Civil & Civic, the construction firm who built St Vincent's Private Hospital. The contribution of Mr Richard Hammond from Civil & Civic was quite remarkable. He was assisted by Mr Richard Bate and the group also had the assistance of Mr Jim Baillie on legal issues.

After many lengthy and sometimes difficult meetings with the medical staff at large, approval was finally given for the Clinic to go ahead and this pioneering joint venture between the Sisters of Charity and the doctors was formed. The support of Sr Bernice with the doctors at that time was quite outstanding. The expertise, wisdom and diplomacy of the original Chairman of the Board, Mr Peter Ferris, was fundamental in progression of the development.

The Clinic was opened in August, 1990. Two years later, the St Vincent's Clinic Foundation was established. The objective of the Foundation was to promote and fund research work done within the Clinic and on the Campus.

Both the Clinic and Foundation have grown in strength and prestige over the years. In 2008, the foundation provided $640,000 funding for 16 separate research grants and 2 multi-disciplinary patient-focussed research grants. The list is provided on page 26 of this issue and on the inside back cover is an application form for persons who may wish to make a donation to assist with the continuing research work supervised by St Vincent's Clinic Foundation. It should be noted that the Ladies Committee of St Vincent's Private Hospital and St Vincent's Clinic Foundation continue to actively support the raising of funds for the Foundation.

The development of the Clinic would not have been possible for the Mission of the Sisters of Charity without the inclusion of the Sisters of Charity Outreach Centre. Sr Bernice was instrumental in the inclusion of the Outreach Centre within the Clinic and it too started from nothing to become the wonderful charitable organisation that it is today.

It can be said that the two major pioneers of St Vincent's Clinic were Sr Bernice and Dr John Roarty (pictured above) and commemorative portraits to both of them rightly hang on level 4 of the Clinic.

This twentieth issue continues the tradition of the Clinic serving as a forum for continuing education and contains seven excellent articles.

Dr Eva Segelov describes the challenges faced and the processes adopted in the current training of our medical students.

Dr Jane McCrohan and Associate Professor Michael Feneley wrote the first of two cardiology articles, their article describing the new technology of multi-slice CT scanning in the evaluation of a range of cardiac conditions and in particular the coronary arteries. In the second article, Associate Professor Diane Fatkin discusses atrial fibrillation, an arrhythmia increasingly prevalent in the ageing population and, untreated, a major risk factor for stroke in that population. She looks particularly at the role of genetics in the development of atrial fibrillation and she was supported in that work by the St Vincent's Clinic Foundation.

Dr Stephen Tisch is a newly appointed neurologist to the Campus, returning from post-graduate studies in the UK where he obtained special training in the medical and surgical management of Parkinson's disease and other movement disorders. His article provides an overview of the management of Parkinson's disease.

Dr Nigel Biggs, ENT Surgeon and Edwin Szeto, specialist in nuclear medicine, have provided learned articles on, respectively, the current management of acoustic neuroma and the use of radio-immunotherapy in the management of Non-Hodgkin's Lymphoma.

Finally, Dr Andrew Field, Cytopathologist with Sydpath, describes his involvement in the teaching of cytopathology in third world countries and the benefits derived therein.

Associate Professor
Eva Segelov

Update on Medical Education

Introduction

Over the past decade there have been major changes in medical education in universities and postgraduate colleges relating to curriculum content, mode of delivery, and assessment. Australian medical schools have followed international trends by updating their programs, adapting to the needs of both learners and teachers in the era of modern technology. This article describes some of the major changes in medical education and relates them to current programs within the St Vincent's Clinical School of Faculty of Medicine, University of New South Wales.

Change in Pedagogy

Medical education has modernized to keep pace with the changes in general education theory that have impacted on learning and teaching in primary and high schools, as well as recognizing the role of education in post-University continuing professional development. Some pedagogical changes include:

- The concept of training students to be life long learners, with recognition of career-long continuation of professional development;[1, 2]
- Recognition that not all learning styles are similar, as with teaching styles, but that increased student engagement in active-mode learning leads to more effective outcomes and development of critical thinking skills;

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'Give a man a fish and you feed him for a day. **Teach a man to fish** and you feed him for a lifetime.'

Chinese proverb

- Recognition that such topics as ethics, professionalism, teamwork, cultural sensitivity, communication skills and reflective practice can be taught and assessed, at least in part; [3, 4]
- Embracing huge changes in technology, particularly electronic media;
- Recognition that continued professional development and teacher support is needed to enhance effectiveness of teachers in medicine, requiring resources and expertise.[5, 6]

Concurrently, changes in both workplace and workforce have driven need for educational reform. In medicine, these include:

- Worldwide workforce shortage, affecting most areas of medicine as well as nursing and allied health;
- Lifestyle changes and emphasis on work-life balance;
- Demographic shift with growing ageing population;
- Redistribution of health care provision into community and outpatient settings;
- Introduction of new technologies in diagnosis and treatment e.g. MRI, molecular diagnostics etc;
- Opening of multiple new medical schools (by 2009, Australia will have 19 universities offering a medical degree, each with different entry criteria and varying mission statements and desired outcomes).

Selection

It is not denied that to study medicine, "high academic ability is essential",[7] but rather that this alone is insufficient. The challenge is to adopt tools which robustly measure both cognitive and non-cognitive abilities, such that they predict not only for performance during the course but also as a medical practitioner.[8,9] Most Australian universities now admit students based on aptitude testing through the national UMAT (Undergraduate Medical and Health Sciences Admission Test)[10] or GAMSAT (Graduate Australian Medical School Admissions Test).[11]

In addition, most medical schools require an interview, either semi-structured of 30-60 minutes duration with two-three panel members (medical and lay), or the Multistation Mini Interview (MMI), an OSCE-style (Objective Structured Clinical Examination) series of around eight stations of 5-10 minutes duration, manned by individual interviewers. Interviews can assess fluency and comprehension of spoken English and allow community input. Some degree of standardization can be achieved with interviewer training and structured marking criteria. However, the process remains subjective, with potential for gender, cultural and other biases. Caution is also given regarding testing attitudes and ethics that may in fact be learned during the course. The influence of coaching (not uncommon in such a competitive environment) is unmeasured, a problem particularly as the resource intensive nature of the interview process does not easily allow for significant changes from year to year. Above all, the predictive validity is uncertain, although many studies are underway relating interview performance to subsequent student grades and as a predictor of later clinical performance. Recent data suggest that MMI have better predictive power and are more cost and time efficient.[8]

Quotas to promote entry of students from under-represented and disadvantaged community groups exist for most Australian medical schools, partly driven by Commonwealth funding models for university places. The aim is to produce doctors from various cultural, geographical and socially disadvantaged populations, as it is thought that such students will return to serve the community they represent. Early results show a higher return to local communities from student educated at rural medical schools.

For the six year undergraduate medicine course at UNSW, entry is by application with an initial short portfolio. The three components: interview, UMAT, and HSC (or equivalent) contribute equally to the final ranking. Conjoint staff are encouraged to become interviewers, with training provided. There is a scheme for entry of rural students, indigenous students and students accepting bonded places (commitment to work in areas of need after substantive training completed).

Curriculum content and organisation

The traditional model of teaching basic biological sciences before progressing to clinical sciences has been replaced in modern medical schools by integration of these around clinical scenarios. There is ongoing, heated debate (e.g. the optimal amount of anatomy teaching) but there is also recognition that the scope of medical education has broadened. Not only are there many new diseases, diagnostics and therapeutics, but globalization has led to more emphasis on public and international health, medical error, health systems and health economics. Exposing students to subjects such as ethics and legal, professionalism, evidence based medicine and skills for life long learning (library and internet skills) has broad practical implications e.g. gaining consent, dealing with patients taking alternate therapies, etc.

Modern curricula have well defined outcomes and detailed learning plans by which these can be achieved. This is an advance over old syllabi which tended to be an exhaustive list of diseases about which students needed to 'know everything".

In 2004, UNSW launched a totally revamped, strongly science-based six year undergraduate curriculum, with outcomes articulated by well defined graduate capabilities grouped under three main headings: Applied Knowledge and Skills, Interactional Abilities and Personal

"We did dissection every Monday from 11-5 and then again on Thursday afternoons, and I don't think I learned anything at all"

name withheld, GP

Attributes (http://www.med.unsw.edu.au). As well as core terms in Medicine, Surgery, Women's and Children's Health, Psychiatry and Community Health, students have the opportunity to select terms in areas of interest in senior years. There is a 32 week research project (the Independent Learning Project) which can be undertaken in any relevant field. St Vincent's Clinical School is a popular choice for a wide variety of clinical and basic research projects.

Method of Delivery

The most well known of the new curriculum designs is Problem Based Learning (PBL), which was a radical departure from traditional didactic teaching. The principles are to instill a useable knowledge base, skills in problem solving, self-directed learning and collaboration. This is achieved through case based, integrated learning using the student's own enquiry, often in small groups facilitated by a tutor, with specified learning objectives. Group work is also a feature to aid practice in the workplace which involves being part of a team.

Most contemporary Australian medical curricula have adopted these principles, which mirror changes in primary and high school education theory and tertiary education in many other faculties. Research is ongoing comparing 'new' and 'old' curricula showing benefit for the newer methods.[12, 14]

Delivery mode has also changed, with two main drivers:

1. e-learning: the advent of internet has revolutionized education in many ways, for example: unprecedented access to learning materials; content delivery at timing and location of student's choice; facilitating communication between individuals and groups of students and staff; etc.[15] Technologies such as videoconferencing and blogging, have also changed the landscape. There is a growing body of evidence (even randomized controlled trials!) that incorporating these technologies are effective.[16]

Lectures at UNSW are podcast and there is emphasis on web based provision of learning materials. St Vincent's Clinical School has a videoskills program where paired groups of students video their performance of a history and physical exam on a patient, with immediate playback. Our handheld transponders allow instant anonymous feedback for formative testing. UNSW encourages professional development for conjoint staff to maximize use of modern technologies in teaching.

2. Simulation: there is solid evidence on the benefit of simulation in learning.[17] This ranges from use of models for learning and practicing procedural skills (e.g. basic and advanced life support, urinary catheterisation, lumbar puncture), to the use of surrogate patients to teach examination skills (e.g. breast and gynaecological assessment).[18] Use of surrogate and standardized patients has been shown to enhance reliability of assessment during clinical exams.

St Vincent's Clinical School is a key stakeholder in the Don Harrison Patient Safety Simulation Centre, with an extensive program of clinical skills taught across all Phases of the New Medicine Program in the simulated environment. Standardized patients are used in some stations of the clinical examination, to compare performance of students across the clinical schools of the Faculty of Medicine.

Assessment

This is also an area of major change with recognition of the need for formative assessment (designed to give continuous feedback to both students and teachers on their progress towards the development of knowledge, understanding, skills and attitude) as well as summative assessment (tasks designed to determine grades or marks at a certain time point).[19] New assessment tools have been introduced into both student and post- graduate medical evaluation, with more emphasis on multisource feedback and broad assessment including professionalism, ethics, teamwork and communication skills.[20, 21] Whilst research into these new tools shows superior predictability and reliability, it is recognized that they are time consuming. Two commonly used modern assessment tools are:

1. miniCEX (mini-Clinical EXamination) – currently used to assess international medical graduates and one of the mechanisms currently being piloted for standardized assessment of all Junior Medical Officers. It involves direct observation of the performance of a task (history or physical examination or procedural skill or communication) with immediate verbal and written feedback. The whole process should take no more than 15 minutes but should be repeated on multiple occasions with different tasks to ensure reliability.

2. RIME paradigm – originally developed in the VA system in the USA, this is a framework of feedback to the learner along a pathway of development as a professional; from Reporter (describes what is happening) to Interpreter (interprets what is happening) to Manager (takes action) to Educator and Evaluator (reflects on performance and teaches others), this uses constructive language to advance students, recognizing the concept of life long learning.

The New Medicine Program at UNSW, which reaches full implementation across all three Phases in 2009, uses a number of modern assessment tools including mini-CEX to allow students to receive feedback on their performance. Peer feedback is also encouraged. St Vincent's Clinical School has run pilot student programs using the RIME mechanism. Training in new assessment methods is available at out regular Train the Trainer workshops.

Medical education research

Medical education research has come of age as a valid area of investigation and scholarship. Qualitative and quantitative studies measuring the impact of various teaching strategies are published in high quality medical education journals such as Medical Teacher and Academic Medicine. There is also a growing interest in publishing medical education articles in journals such as BMJ and MJA. Medical education research projects attracting competitive research funding with recent creation of specialized categories within the NHMRC and ARC granting codes for medical education research. National and international conferences are well attended by all stakeholders in health professional education so that future changes can be evidence-driven. Measuring educational outcomes is a challenging and relevant to a wide range of health professionals who are facing similar challenges in their professional education and development programs.

Evaluation of the New Medicine Program at UNSW is ongoing, recognizing that measuring educational outcomes is complex. New teaching methods are trialled and rigorously evaluated,[22] under the direction of the Program Evaluation and Improvement Group. Long term impact is of particular importance.

Summary

Many changes have driven the evolution of medical education internationally from didactic, teacher based curricula to student-centered curricula focussing on teaching lifelong learning skills. Many different types of learning packages defined by specific learning objectives and outcomes, with corresponding assessment, have been developed. Although these changes may at face value be challenging to our own educational pedagogy, it is anticipated that students will develop skills that will allow them to manage the demands of modern medical practice.

The St Vincent's Clinical School welcomes appointment of conjoint staff and encourages all consultants across the campus to become affiliated. In particular a focus on one-on-one teaching of senior students in private rooms during consultations has been successful over the past several years, with excellent feedback from students and consultants. A survey of patient attitudes is planned for the near future but most consultants report that patients welcome students in these controlled conditions. For further information, please see http://www.med.unsw.edu.au/medweb.nsf/page/Conjoints, or contact the Clinical School 83822023.

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Coronary CT – Will it change the way we practice cardiology?

Assoc Prof Jane McCrohon
Professor Michael Feneley

Introduction

Dramatic improvements in technology have occurred in the last decade across all cardiac imaging modalities but perhaps none has better commanded the attention of the medical fraternity than that of cardiac CT. This review will provide an overview of the current state of play in the use of this technology in clinical practice and where new developments in scanner technology are likely to lead over the next few years. At a time when the St Vincent's campus is rapidly developing its cardiac imaging program, the future looks bright in terms of our ability to bring cutting edge techniques in imaging to the diverse range of cardiac patients in our care.

Background

Cardiovascular disease is the leading cause of mortality worldwide[1] with atherosclerosis as the major contributor in this process. Atherosclerotic lesions develop through stages from fatty streaks to plaques of varying morphologies. These plaques may be obstructive (flow limiting and often symptomatic) or non-obstructive; stable or unstable (based on the content of lipid and inflammatory components) and either fatty, fibrous or calcific in nature (or a combination of these).

In the diagnosis and management of coronary artery disease, we have traditionally relied on functional assessment or stress tests (exercise ECG, stress echo or myocardial perfusion scans). Different methods of stress assessment use different end points to assess flow reserve of the myocardium. When a stress test is performed to investigate the possibility of coronary artery disease, we are assessing the presence or absence of a flow limiting stenosis of sufficient severity to induce myocardial ischaemia and its accompanying sequelae in the 'ischaemic cascade' (diastolic dysfunction, perfusion deficits, reduced myocardial systolic thickening, ECG changes and finally patient symptoms of chest tightness, effort intolerance and/or dyspnoea). Functional assessment therefore relies on the existence of significant coronary artery narrowing (usually >70 per cent luminal narrowing) with a sufficient reduction in myocardial blood flow during stress to yield a positive result. The accuracy of different tests varies across different populations based on the clinical likelihood of disease and other patient factors. Depending on the presence and extent of myocardial ischaemia and/or patient symptoms, many patients will then be referred for invasive coronary angiography and potential revascularization.

Unfortunately, as many as half of first coronary events (including myocardial infarction and death) occur in previously asymptomatic people[2] and occur due to the rupture of unstable non-occlusive plaques which cannot be detected with functional assessment alone or even conventional invasive coronary angiography. This concept is not new and was well defined by Glagov in 1987 whereby there is outward or 'positive' arterial remodeling of the arterial wall and preservation of lumen size until 40

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per cent or greater of the internal elastic area is affected by atheromatous plaque **(Figure 1)**.[3] It is now recognised that these types of plaques are frequently unstable and their detection is now possible with new modalities such as intravascular ultrasound (IVUS), magnetic resonance and most recently CT. CT coronary angiography (CTA) therefore provides additional information beyond the lumen and although not promoted as a screening test for asymptomatic low risk individuals, may provide an opportunity to better risk stratify our patients at intermediate coronary risk.

The paradigm for cardiac CT use and its integration with other imaging modalities remains in evolution and is likely to change as the technology and our familiarity with the technique increase. Current recommendations or clinical appropriateness criteria (REF) have been provided by various international bodies such as the American College of Cardiology and Radiology (ACC and ACR) and the Society of Cardiovascular Computed Tomography (SCCT) and the main indications for cardiac CT at this point in time are summarized in **Table 1**.

Whether CTA should be done as an initial test in a patient with symptoms suggestive of coronary disease or used as a 'gatekeeper' following functional testing is indeterminate. Recent work has suggested that regardless of the anatomical accuracy of a technique (CT or conventional angiography), there is often a poor correlation between the angiographic stenosis grade and the functional effect on downstream flow to the myocardium and patient symptoms.[4] Functional testing prior to treatment is therefore likely to remain a key component in patient management in the years ahead. Emerging prognostic data for CT and correlation of clinical outcomes based on test accuracy will influence these decision processes, as will the potential for simultaneous CT assessment of myocardial perfusion which could finally provide the coveted holy grail of anatomical and functional evaluation of coronary disease in a single test. The role of integrated imaging, such as PET-CT, as a provider of both functional and anatomical information in a single examination is also being explored.

The Fundamentals of CT

CT images are generated by ionizing radiation. An x-ray beam passes through the body at different angles and is received by a detector array on the other side of the patient. The x-ray beam reaching the detector array is digitized to produce pixels of a known size and each pixel contains gray scale information

Table 1: *Current appropriate indications for Cardiac CT**

EVALUATION OF CHEST PAIN SYNDROME INTERMEDIATE PROBABLITY GROUP
ASSESSMENT OF CORONARY ARTERY ANOMALIES
EQUIVOCAL OR UNINTERPRETABLE STRESS TEST
EVALUATION OF CORONARY ARTERY BYPASS GRAFTS
CONGENITAL HEART DISEASE
EVALUATION OF CORONARY ARTERY DISEASE IN NEW ONSET HEART FAILURE
EVALUATION OF CARDIAC MASS / PERICARDIUM
PATIENTS WITH LIMITED IMAGE QUALITY FROM OTHER TECHNIQUES
PULMONARY VEIN, CORONARY VEIN MAPPING
ASSESSMENT OF GREAT VESSELS

* *Adapted from Reference 6*

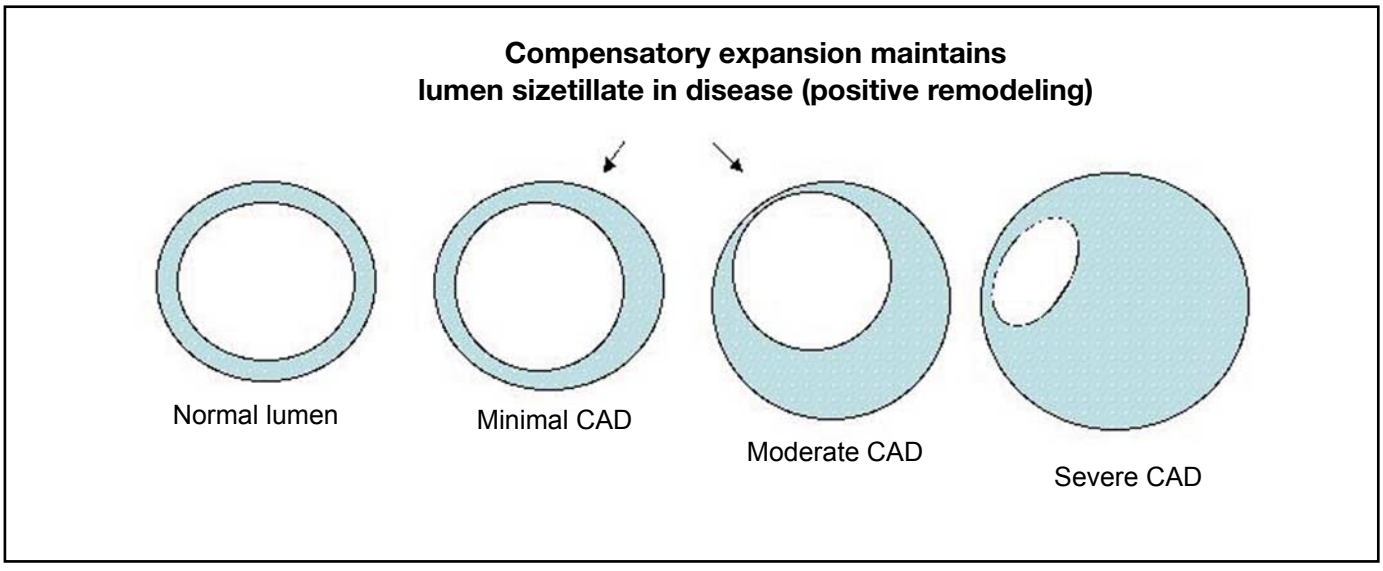

Figure 1: The Glagov Phenomenon
Traditional lumenal angiography will only detect disease that encroaches the lumen. In the presence of positive remodeling of the arterial wall in atherosclerosis, lumenal area can be preserved and labeled as 'normal' on catheter angiography even in the presence of significant plaque burden. In contrast, CTA can clearly visualise the entire spectrum of atherosclerotic remodelling

based on the beams attenuation through different tissues. This attenuation information is represented in Hounsfield Units (HU), and ranges widely from air (-1000HU) to water (0HU) and bone cortex (+1000HU).

Cardiac CT is usually performed on a multislice CT (MSCT) scanner with a rotating x-ray source and stationary detector arrays. Continuous or stepwise table movement allows the collection of a volume data set. Recent developments in scanner technology have seen a rapid increase in the number of slices acquired per breath hold from 4, 16, 64 and now 256 and 320 slice acquisitions. Such developments along with increased gantry speeds and improved acquisition and reconstruction techniques have led to improved coverage, faster scan times and increased temporal and spatial resolution. Current scanners now achieve isotropic voxels of 0.35mm^3 and temporal resolution from 40-200ms (compared to spatial and temporal resolution of 0.1-0.2mm and 5-10ms, respectively, with catheter angiography).

Patient preparation is essential in coronary CT, with most centres advocating heart rates of <65 beats/min (using oral or IV beta blockers as tolerated) and sublingual nitroglycerin to improve vessel calibre just prior to scanning. Images are acquired during a single breath hold which may vary from 5-20 seconds depending on the scan protocol. ECG gating of the image acquisition may be retrospective or prospective, with the best images usually acquired in diastole when the heart is still. A single intravenous injection of iodinated contrast (usually 70-100ml based on body size) is administered during the breath hold scan.

From the hundreds of images obtained, analysis is largely performed from the raw 2D slices which constitute the 3D acquisition and from multiplanar 'reformats' of each artery in different views. Cross-sectional analysis of lumen size and plaque morphology can be performed. The maximum intensity projections (MIP) and 3D rendered images, while visually attractive, are less useful in the analysis of stenoses and plaque characteristics **(Figure 2)**.

Diagnostic accuracy

Although the latest generation of scanners (256/320 slice) are still being evaluated, data from 64 and 16 slice MDCT has confirmed the high negative predictive value of coronary CTA (>97 per cent). This confirms its key role in the 'ruling out' of significant disease. It is important to remember, however, that much of this data was acquired in single-centre studies with a high level of expertise and variable patient populations. Perhaps the most meaningful clinical accuracy data has emerged from the CORE 64 CT trial, which was a multicentre, 'real world' trial of patients scheduled to have invasive catheter angiography. The prevalence of disease in this trial was 56% (much higher than in other studies) and much higher than many of the patients currently being sent for CTA in many centres. The performance of CTA even in this higher risk group was very good, with sensitivity, specificity, positive predictive value and negative predictive value of 85, 90, 91, and 83%, respectively, when compared with invasive angiography.[5]

Factors associated with reduced diagnostic accuracy include the presence of heavy calcification, rapid or irregular heart rates (atrial fibrillation or ectopics) and inadequate breath holding technique. Although there will always be some limitations, many of these are becoming less problematic with developments in technology and more rapid acquisitions.

Minimising radiation exposure has been a key concern leading to techniques such as x-ray dose modulation based on body size and ECG modulation, where the tube current is maximal or turned on only during the diastolic phase(s) of interest. One of the latest generation scanners, a 320 slice CT scanner, is capable of acquiring data within a single heart beat using prospective gating and only 10-30% of the R-R interval, producing radiation levels as low as 4-7mSv for coronary angiography and 1mSv for coronary calcium scoring. Similarly low radiation doses can be achieved, albeit over a minimum of two heart beats, using prospective gating on the 256 slice scanner. This compares with 6-10mSv radiation dose for invasive diagnostic catheter coronary angiography and 15-20mSv for nuclear SPECT perfusion imaging.

As with any CT examination, children and females are at greater risk of radiation exposure and knowledge of renal function and diabetic status are essential to minimize the risk of contrast nephropathy.

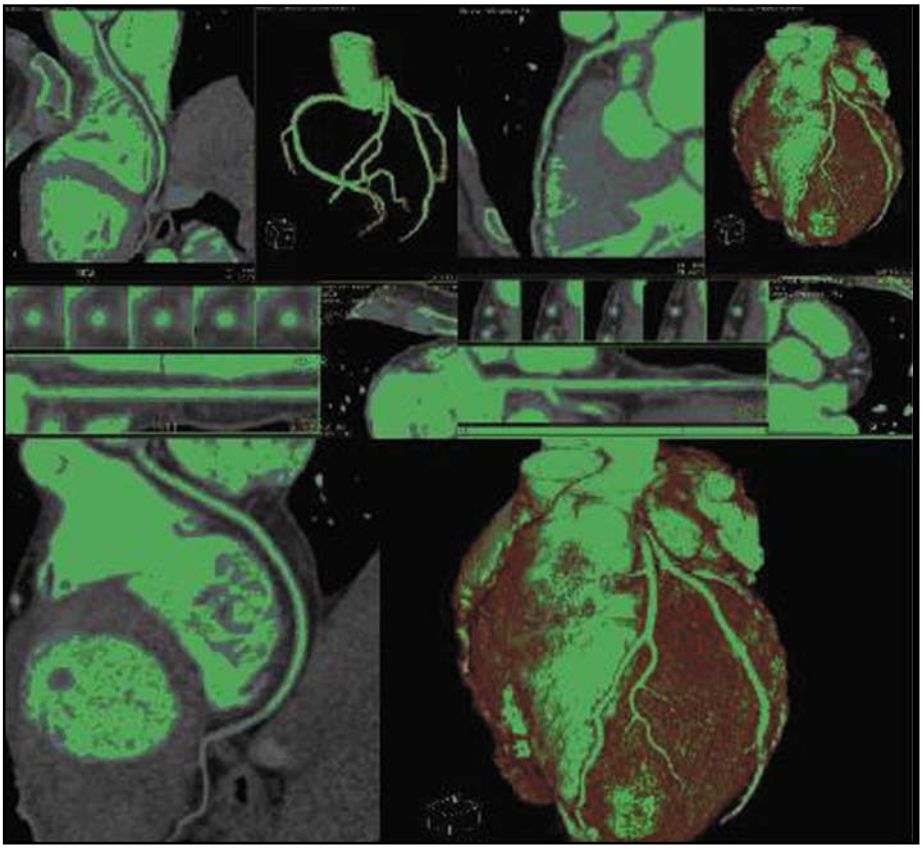

Figure 2: *Analysis of CT coronary angiography data involves a detailed review of 2D, 3D and cross-sectional images*

Coronary Artery Calcium Scoring

This is usually performed as a single breath hold scan just before the CTA acquisition, and is a low radiation, low resolution scan. Most reports define the calcium score based on the patient's age and gender, and place the patient in a quartile of coronary artery disease risk based on previous data registries **(Figure 1)**. Stated simply, a calcium score of zero is associated with an extremely low likelihood of significant coronary atherosclerosis (although not zero, particularly in younger patients) and >400 with a high likelihood of extensive atherosclerosis.

Recent data have suggested that coronary calcium scores provide incremental risk stratification in individual patients beyond that offered by the Framingham Risk Score alone. For example, in one study, 45% of patients having a high Framingham Risk Score could be reclassified into low or intermediate risk by their coronary artery calcium scores.[7]

Interestingly, despite the correlation of increasing calcium score with age and atherosclerotic burden in a given individual, calcium within a plaque is more likely to represent stable or slowly evolving pathology, whereas minor specks of calcium or its absence is felt to be characteristic of the more lipid-rich plaques associated with less stable plaque physiology. The role of calcium scoring and plaque characterization is an area of intense research interest at this point in time using CT and other techniques such as intravascular ultrasound and MRI.

Multimodality Cardiac imaging – the role for coronary CT

It is now well recognised that any new technology should be demonstrated to provide incremental information and improvements in patient care over existing techniques before its routine use is recommended. In cardiology, techniques such as nuclear medicine have provided us with a wealth of prognostic information over many years. Such information has been used to draw conclusions and develop similar data in new modalities such as MRI and CT. Prognostic and cost-effectiveness data for coronary CT are rapidly emerging, and will no doubt shape the use and reimbursement of this technology in the years ahead.

The available information does not currently support the routine clinical application of CT coronary angiography in asymptomatic individuals, although research studies exploring its possible role in low, intermediate and high risk asymptomatic subjects are in progress. The technique is still in its early stages and long-term follow up will be needed before a screening use of coronary CT is likely to be embraced.

Two recent studies have clearly shown that the extent and severity of coronary atherosclerosis on coronary CT is associated with a worse prognosis when compared with the absence of coronary atherosclerosis.[8,9] In particular, a worse prognosis was associated with more proximal disease, stenoses >50 per cent, the number of arteries involved and the presence of left main disease. The scoring used to assess plaque severity and extent across all branches of the coronary tree was shown to predict all-cause mortality independently of other traditional risk factors. The fact that >50 per cent of myocardial infarcts occur on non-occlusive plaque is probably largely related to the higher incidence of these plaques overall, with the study by Min et al[8] confirming that those patients with the greater extent of plaque (independent of stenosis severity) had a poorer prognosis. Conversely, the study also confirmed that the absence of coronary plaque conferred a high negative predictive value of 97.8-99.7% for events over the 15 month average follow-up period.

The Future

Cardiac CT will continue to evolve rapidly over the next few years due to its accessibility, ease of use and preference by patients and referrers for a non-invasive means of visualizing the coronary arteries. It is unlikely however, that anatomical imaging alone will provide sufficient guidance in many cases where disease is present and in the patient population most cardiologists review in their rooms. Supplementary functional imaging will be required to guide management decisions after many abnormal CT scans, but the emerging technique of CT myocardial perfusion imaging offers a golden opportunity for a truly comprehensive single test for ischaemic heart disease. Whether the technology meets expectations remains to be seen, and how we incorporate the range of cardiac imaging modalities now available to us into improved patient care is likely to be even more important in years to come than the technology itself.

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Update on the Medical and Surgical Management of Parkinson's Disease

Dr Stephen Tisch

Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder with a prevalence in Sydney of 3.4 per cent in people aged 55 years or over.[1] PD is characterised by the cardinal motor symptoms of tremor, rigidity, bradykinesia and gait disorder with postural instability. Levodopa remains the most effective oral medication for the motor symptoms of PD but is associated with the development of motor complications including dyskensias and ON/OFF phenomena usually within 3-5 years of treatment. Motor complications from Levodopa are worse in younger patients and when higher doses of Levodopa are used.[2] The increased recognition of levodopa induced motor fluctuations and the availability of alternative dopamine agonist therapies has led to a reappraisal of both early and later treatment of PD. For those patients with advanced PD and established motor fluctuations, significant treatment advances have been made with the use of continuous Apomorphine infusion or deep brain stimulation (DBS) surgery. As treatments for motor symptoms of PD have improved, there has been increased recognition of residual non-motor symptoms affecting cognition, sleep, mood, autonomic and sexual function which may contribute to disability. These aspects may also be improved with specific pharmacotherapy and interventions. In this review treatment strategies for early and advanced PD will be presented with an emphasis on pharmacotherapy and surgery available within the Australian context. The major limitation of current available treatment options for PD is the lack of neuroprotective or neurorestorative therapy, and future therapies in development will also be discussed.

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Levodopa and Motor Fluctuations

Levodopa was first used for PD in the early 1970s and remains the most effective oral dopamine replacement medication for the motor symptoms of PD. It has never been subjected to a randomised controlled trial. Unlike North America where Sinemet (Levodopa/carbidopa) is the only available Levodopa preparation, Australia like Europe has Madopar (Levodopa/benserazide) which is very useful since occasional patients will tolerate one but not the other. Motor fluctuations occur in about 10 per cent of Levodopa treated patients with each year of treatment, so that by five years about 50 per cent are affected. Levodopa has not been shown to be toxic to dopaminergic neurons in vivo nor does it accelerate the neurodegenerative process, rather motor fluctuations arise due to sensitizing plasticity with the striatum due to pulsatile dopminergic stimulation. Motor fluctuations consist of dyskinesias (choreoform, dystonic, diphasic), wearing off and end of dose deterioration, ON/OFF phenomena, delayed ON and dose failures. Patients may undergo frequent rapid transitions between a rigid immobile OFF state and a mobile ON state, which may be further compromised by dyskinesias. The development of motor fluctuations often heralds an escalation in disability and dependency, particularly when frequent severe OFF periods cause immobility and falls or severe dyskinesias interfere with function during the ON phase. Motor fluctuations are more likely to develop in younger patients and after 6 years of treatment affect almost 100 per cent of patients with PD onset < 40 years. Larger doses of Levodopa promote the

development of motor fluctuations. In the ELLDOPA trial the rate of dyskinesia was 2.3 per cent in patients treated with 300 mg/d of levodopa and 16.5 per cent with 600 mg/day after nine months of treatment.[3] The use of lower Levodopa doses particularly in early PD has reduced the incidence of severe motor fluctuations. Despite the limitations of Levodopa it is the most potent oral dopamine replacement therapy and forms the mainstay of treatment for most patients.

Catechol-O-Methyl Transferase Inhibitors

Catechol-O-methyl transferase (COMT) inhibitors reduce the peripheral degradation of Levodopa thereby boosting levels reaching the brain. COMT inhibitors prolong the action of Levodopa and reduce end of dose wearing off. The down side of COMT inhibitors is that they may exacerbate dyskinesias. Other side effects include diarrhoea and harmless brown discolouration of the urine. Entacapone (Comtan) is co-adminstered with some or all of the daily Levodopa doses, and is typically initiated when patients begin to experience end of dose wearing off. The combined Entacapone Levodopa/carbidopa preparation (Stalevo) is preferred by many patients[4] and is finding an increasing role in the initial treatment of PD in the hope that lower Levodopa total dose and more continuous dopaminergic stimulation may forestall motor fluctuations, however, to date this is unproven. Tolcopone, a potent and efficacious COMT inhibitor was withdrawn in Australia in 1999 due to cases of fatal hepatotoxicity. It is more effective than Entacapone in increasing ON time and may have limited role in Entacapone refractory patients provided careful monitoring of liver function is performed.[5,6]

Monoamine Oxidase B Inhibitors

Monoamine oxidase B inhibitors (MAO-B) also enhance the effects of Levodopa by inhibiting brain enzymatic degradation of dopamine and blocking reuptake of dopamine at the synaptic cleft. Unlike COMT inhibitors MAO-B do not require co-administration of Levodopa to produce symptomatic improvement and are sometimes used as first line treatment for mildly affected PD patients and delay the need for Levodopa by about nine months.[7] More commonly MAO-B are used as adjuvant therapy in Levodopa treated patients to reduce OFF time, but may worsen dyskinesias, psychotic phenomena or provoke postural hypotension. A prospective UK study showed a higher five year mortality among patients treated with a combination of Selegeline and Levodopa[8] however other studies have not shown increased mortality. Rasagaline is a highly bioavailable irreversible MOA-B inhibitor is available in Europe and North America but not yet in Australia. As adjuvant therapy Rasagaline prolongs ON time by about 25 per cent[9], an effect comparable to that of Entacapone.[10]

Dopamine Agonists

Dopamine agonists include the ergot derived agents (Bromocriptine, Pergolide, Cabergoline) and the synthetic non-ergot agents (Ropinirole, Pramipexole, Rotigotine, Apomorphine). The literature surrounding dopamine agonists is extensive but a few key points can be made, and are supported by a recent Cochrane review.[11] As monotherapy the dopamine agonists are less potent than Levodopa but have a lower incidence of motor fluctuations particularly dyskinesias. Dopamine agonists induce side effects including nausea, postural hypotension, somnolence, hallucinations and behavioural dysregulation (in particular pathological gambling), to a greater extent than Levodopa. Dopamine agonists are useful as first line treatment in younger patients and those with milder symptoms, to postpone the requirement of Levodopa. In addition they are valuable as adjuvant treatment in Levodopa treated patients to reduce motor fluctuations by increasing the duration and quality of ON time, sometimes at the expense of worsening dyskinesias. Within the Australian context Pramipexole (Sifrol) in June 2008 became the first non-ergot dopamine agonist PBS listed for PD. This development is of heightened significance because of increasing safety concerns surrounding the ergot agonists which may cause cardiac valvulopathy,[12,13] and are being phased out, where possible in the majority of patients. Older agonists can be successfully switched overnight to a corresponding dose of non-ergoline agonist.[14] Rotigotine is a potent novel dopamine agonist administered as a transdermal patch applied every 24 hours with potential advantages in terms of continuous dopaminergic stimulation and patient preference. Initial experience of Rotigotine has been very positive.[15] It is licensed in Australia, but is expensive and is not yet PBS listed.

Apomorphine

Apomorphzine was first synthesised in the 1850s by the reaction of morphine with hydrochloric acid and was originally marketed as an emetic. It has no narcotic properties but is a high potency dopamine agonist with affinity to D1 and D2 receptors. It is the only dopamine agonist with a magnitude of clinical effect on motor symptoms equivalent to Levodopa. Apomorphine is not orally bioavailable and has a short half life and therefore requires subcutaneous administration either as intermittent injections or continuous subcutaneous infusion. Because Apomorphine is emetogenic, premedication with Domperidone is required. Intermittent Apomorphine injections are useful as "rescue" therapy for OFF periods, providing rapid improvement in mobility. Patients with more frequent OFF periods and dyskinesia benefit more from continuous infusions, which increase ON time by about 50%, and reduce dyskinesias, particularly in those patients able to discontinue Levopdopa.[16-18] The infusion is usually limited to the waking day, but can in some circumstances be given 24 hours a day. Apomorphine infusions require a small infusion pump to be worn **(Figure 1)** and inpatient initiation by an experienced team. Once established, the infusions are usually trouble free. Some patients develop skin nodules at the injection sites and occasional haemolytic anaemia can occur. Apomorphine is licensed in Australia for intermittent injection and continuous infusion and is PBS listed.

Amantadine And Anticholinergics

Amantadine is a non-competitive NMDA receptor antagonist, and the only class of drug which acts on brain glutamate receptors which are known to play an important role in PD. It has modest intrinsic antiparkinsonian effects and is sometimes used as a first line drug in mildly affected patients however the beneficial effects are often unsustained. More recently its anti-dyskinetic properties have been recognised. When used as adjuvant therapy Amantadine reduces dyskinesias by up to 50-60 per cent.[19,20] Problems with Amantadine include insomnia, confusion and ankle oedema.

Anticholinergic agents including Benzhexol (Trihexphenidyl) and Benztropine are probably underutilised and provide an alternative initial monotherapy in mildly affected or tremor dominant patients.[7] Atropine-like side effects and worsening of psychotic or cognitive aspects limit their usefulness and make them unsuitable the elderly.

Medical Management of Motor Fluctuations In PD

Early motor fluctuations such as end of dose wearing OFF can be managed initially by shortening the Levodopa dose interval. Peak dose dyskinesias may respond to a reduction of individual Levodopa doses. Delayed ON or dose failures may be helped by taking Levodopa 30-60 minutes before food and eating smaller more frequent meals to offset competitive inhibition of Levodopa protein transport at the gut and brain. Similarly, dispersible Levodopa preparations (e.g. Madopar rapid) may be useful to hasten the onset of Levodopa effect. Nocturnal OFF periods can be treated with slow release Levodopa (e.g. Sinemet CR) at bedtime and additional immediate release Levodopa during the night. When manipulation of Levodopa fails to control increasing OFF periods, the addition of Entacapone or the introduction of a dopamine agonist is usually beneficial, however these agents may worsen dyskinesia. However, dopamine agonists and COMT inhibitors may allow reduction of total Levodopa dose, which over time can help reduce dyskinesias. A common mistake when adding agonists is to use too low a maintenance dose. The starting doses are low to avoid side-effects particularly nausea and hypotension, and adequate upward titration should be performed until a therapeutic effect is achieved or side effects are reached. Dyskinesias can be treated directly by the addition of Amantadine. Painful OFF dystonia in a limb can be helped in selected patients with botulinum toxin injections. As motor fluctuations worsen combination adjuvant therapy with dopamine agonists and COMT inhibitors can provide additional benefit. Increasingly, such combination therapy is being used earlier in the course of disease in an effort to limit the Levodopa requirement and minimise Levodopa induced motor complications.

When disabling motor fluctuations are no longer manageable with oral medications, intermittent subcutaneous injections or continuous infusion of Apomorphine should be considered. An alternative is continuous duodenal infusion of Levodopa (Duodopa) which in small open label studies has been shown to significantly decrease OFF time and dyskinesias.[21,22] Duodopa requires a jejunostomy tube and infusion pump, and complications related to the tube are common.[23] Duodopa is an orphan drug in Australia and its availability is limited. In the real world the pharmacotherapy of motor fluctuations in PD is challenging because of the complex neuropsychiatric, cognitive, behavioural and autonomic aspects of the disease and in response to drug therapies.

Figure 1. *Programmable Apomorphine infusion pump, which delivers a continuous subcutaneous infusion of Apomorphine via a butterfly needle. The pump is worn by patients in a belt carry case.*

Non-Motor Symptoms and Pharmacotherapy

Non-motor symptoms of PD are diverse and include cogntitive, psychiatric, behavioural, autonomic and sleep disturbances. Cognitive decline and hallucinations may be helped by central acetylcholinesterase inhibitors. Hallucinations, paranoia and other psychotic phenomena may be improved by reducing dopaminergic medications particularly the dopamine agonists and stopping other provocative medications such as anticholinergics. Atypical antipsychotic agents such as Quetiapine and Clozapine which do not worsen motor symptoms are useful. Depression is a frequent problem and useful agents include Amitriptyline and Venlafaxine. Dream enactment behaviour (REM sleep behaviour disorder) is also common in PD and often predates cardinal motor symptoms. It is disruptive and potentially injurious to the sleep partner and usually responds to Clonazepam. Excessive daytime somnolence is common, can be exacerbated by dopminergic medications and Modafinil is useful in some patients. Autonomic problems include constipation, urinary dysfunction, postural hypotension, impotence and sialorrhoea. Detruser hyperreflexia may result in urinary frequency and urgency which usually improves with Oxybutinin. Orthostatic hypotension can be managed by liberalising fluid and salt intake, Fludrocortisone or Physostigmine. Impotence may respond to Sildenafil. Sialorrheoa is usually worse in the OFF state, and optimising dopaminergic medications may be sufficient. Additional treatments include one per cent Atropine eye drops sublingually or botulinum toxin injection into the salivary glands.

Functional Neurosurgery for PD

The development of deep brain stimulation has led to renaissance of functional neurosurgical intervention for PD. Traditional lesional surgeries such as thalamotomy and pallidotomy, although effective, have been almost entirely superseded by DBS, which is safer more adaptable and largely reversible. DBS involves implantation of electrodes using stereoetactic surgical technique to precise targets within the brain. The electrodes are connected to an implanted pulse generator which resembles a cardiac pacemaker and the whole system is internalised under the skin **(Figure 2)**. Chronic high frequency stimulation is delivered which electrically silences the brain target nucleus mimicking the effect of a lesion.

The main targets for DBS are the thalamus, globus pallidus and the subthalamic nucleus (STN). Thalamic DBS is effective for tremor but does not improve rigidity, bradykinesia or gait. It is usually carried out unilaterally, and retains a limited role in asymmetric tremor dominant PD patients. DBS of the medial segment of the globus pallidus is particularly effective for dyskinesia but also alleviates tremor, rigidity and to lesser extent bradykinesia. Surgery is usually bilateral although may be performed unilaterally for the contralateral hemibody. Typically it is not possible to decrease dopaminergic medications after pallidal DBS, and medications may even be increased because of freedom from dyskinesia. Pallidal DBS tends not to provoke neuropsychiatric disturbances and is well tolerated even in older or more severely affected patients. For these reasons the postoperative management is more straightforward and there is a low incidence of complications.

Bilateral STN DBS is the most effective operation to alleviate all the motor symptoms of PD including tremor, rigidity, bradykinesia and gait akinesia. Dyskinesias are also reduced but this effect is progressive and in the short term STN DBS may actually provoke dyskinesia during the adjustment phase. Because of the high efficacy in alleviating motor symptoms, dopaminergic medications can be reduced on average by about 50 per cent which is believed to contribute to the anti-dyskinetic effect.

Which PD Patients Are Suitable For DBS?

DBS is indicated in PD patients with disabling motor fluctuations despite optimal medical treatment. For STN DBS it is very important that Levodopa responsiveness is preserved; the patient must still have good ON phases even if these are short lived or contaminated by dyskinesias. It is well established that STN DBS is not effective in those patients who no longer respond to Levodopa and indeed the magnitude of improvement after STN DBS correlates well with preoperative motor improvement following Levodopa challenge.[24] Gait balance is also very important and those patients with Levodopa refractory postural instability and falls respond poorly to STN DBS. Other important considerations are the patient's age, cognition, psychiatric state, speech, general medical health, expectations, employment and family supports.

Outcomes After STN DBS For Advanced PD

STN DBS is highly effective for motor symptoms of PD in many patients eliminating OFF periods completely allowing patients to resume previous activities or continue employment. The effects are durable and the bulk of improvement is maintained after five years, with some deterioration attributable to underlying disease progression.[25] Large controlled studies have confirmed that STN DBS for PD improves quality of life.[26]

There are a number of potential problems associated with STN DBS. Neuropsychiatric changes can occur including post-op confusion, hypomania, depression, apathy and occasionally suicide.[27] There are minor but measurable changes in cognition after STN DBS mainly concerning reductions of verbal fluency.[28] These changes are not clinically significant, however it is well recognised that in elderly patients[29] or those with pre-existing cognitive impairment[30] marked cognitive deterioration can occur, emphasising the need for careful patient selection. Speech is not consistently improved by STN DBS and in some patients worsens. The dramatic physical improvement can put strain patient's sense of self, family dynamics and relationships and carers

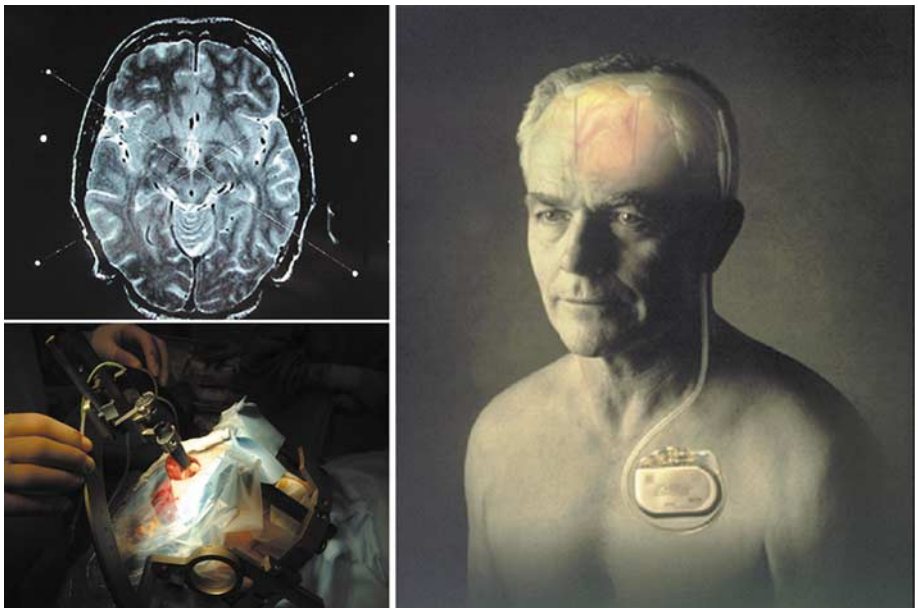

Figure 2. *T2 weighted stereotactic axial brain MRI image showing STN nuclei marked for calculation of sterotactic coordinates. Panel below shows electrode implantation using rigid stereotatic frame. Right panel shows complete DBS system including implanted pulse generator, connecting cables and brain electrodes, which is all internalised under the skin.*

may feel obsolete.[31] With careful patient selection and post-operative adjustment of medications and neurostimulator settings, these problems can be minimised, and the majority of patients do very well. STN DBS requires and experienced team including neurosurgeon, neurologist, movement disorders nurse as well as involvement of neuropsychologist, psychiatrist, speech therapists and allied health professionals. Bilateral STN DBS is the preferred operation for most PD patients and the most widely performed. The selection criteria are more stringent than for pallidal DBS which provides a valuable alternative procedure particularly for those with a predominance of dyskinesias.

Future Directions And Treatments On The Horizon

The existing therapies for PD including DBS are symptomatic and do not modify underlying disease progression. Neuroprotective therapy if started early in the disease or even in presymptomatic individuals might prevent progression of PD neuropathology and the development of clinical disease. Neurorestorative therapies aim to reverse existing pathology by promoting regeneration of healthy neurons. Various treatment strategies have been proposed including antioxidants, fetal nigral transplantation, neurotrophic growth factors and stem cells. Some therapies have reached human clinical studies. Fetal nigral transplantation into the striatum has yielded mixed results with some patients showing dramatic sustained improvement[32] and others developing severe complications including uncontrollable dyskinesias.[33] Infusions of glial derived neurotrophic growth factor (GDNF) into the striatum produced significant improvement in clinical symptoms within three months in five patients with advanced PD and functional imaging showed increased dopamine in the striatum.[34] A larger randomised multicentre study found striatal GDNF infusion ineffective[35] however technical differences in the type of catheter used may have contributed. Delivery of GDNF to the brain using viral vectors and encapsulated cells is also being explored. A recent study using stereotactic injection of adenovirus-associated neurturin (another neurotrophic growth factor closely related to GDNF) in 12 PD patients found significant improvement in the OFF Levodopa motor scores and increased ON time at one year.[36] Stems cells are capable of differentiating into dopaminergic neurons which have been shown to be beneficial in animal models of PD.[37] The effective means of delivery and regulation of stem cells for human PD treatment has not yet been resolved. The issue of tissue and cell transplantation for PD has become more complicated recently by the discovery of distinctive PD neuropathology in longstanding fetal grafted tissue,[38,39] suggesting a potentially transmissible component of PD neuropathology which could pose additional obstacles to successful transplant therapies.

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Atrial Fibrillation – Is it in your Genes?

Dr Diane Fatkin

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and a major predisposing factor for thrombembolic stroke and heart failure. Despite advances in drug therapies and non-pharmacological intervention strategies, effective treatment of AF remains a significant clinical challenge. A better understanding of the causes of AF should open new avenues for diagnosis, treatment and prevention. Recent epidemiological data showing familial aggregation of AF suggest that inherited gene variants are likely to contribute to AF pathogenesis in a significant proportion of cases. Elucidation of the genes involved and the mechanisms linking genetic defects with atrial arrhythmogenesis is a "hot" area of international research in cardiovascular genetics. Our group is studying families in which AF appears as an inherited trait. By studying families we hope to identify key molecular determinants of AF, which will provide a framework for elucidation of disease pathways that underlie the more commonly-occurring sporadic forms of AF.

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Clinical Burden of Atrial Fibrillation

AF is a cardiac rhythm disorder characterised by rapid and irregular activation of the atria **(Figure 1)**. The loss of effective contraction promotes blood stasis and thrombus formation in the atria as well as reduced left ventricular filling. Consequently, AF results in an increased risk of stroke and heart failure.[1,2] AF can occur at any age, but is more common in the elderly, affecting up to 10 per cent of those over the age of 80 years.[3] In individuals aged 40 years, the lifetime risk of developing AF is >20 per cent.[4] Given the increasing proportion of the elderly in our community, together with a rapidly rising number of young people with predisposing factors for AF, the morbidity, mortality and costs of this condition are already high and are predicted to escalate substantially in the future.[5]

Causes of Atrial Fibrillation

There is a long list of cardiac and systemic disorders that predispose to AF development. These include coronary artery disease, valvular heart disease, cardiomyopathies, hypertension, chronic respiratory disorders, diabetes and thyroid disease. In addition to these well-known risk factors, a number of novel risk factors have been identified, including obesity, obstructive sleep apnoea, heavy alcohol intake and psychosocial factors.[6] AF can occur in the absence of any of these predisposing conditions in approximately 10 to 20 per cent of cases ("lone" AF).[7] Genetic factors have not traditionally been considered in the differential diagnosis of AF aetiology.

Familial Aggregation of Atrial Fibrillation

Case reports of families with AF have appeared in the literature since 1936.[8] Despite these observations, familial clustering of AF has often been regarded as coincidental. Two large epidemiological studies have evaluated the prevalence of a family history of AF in community-based cohorts. The first of these was performed in more than 2,200 individuals in the offspring cohort of the Framingham Heart Study in Massachusetts, USA.[9] The investigators found that those individuals who had one or both parents with documented AF had an almost doubled chance of AF development when compared to individuals without a parental history of AF. In a second study of over 5,000 individuals in Iceland, the risk of AF in first-degree relatives of patients with AF was increased nearly two-fold overall, but rose to five-fold when AF in the index case was diagnosed at a relatively early age (<60 years).[10] These two studies demonstrate that a substantial proportion of individuals with AF do have a positive family history. Although familial aggregation can result from

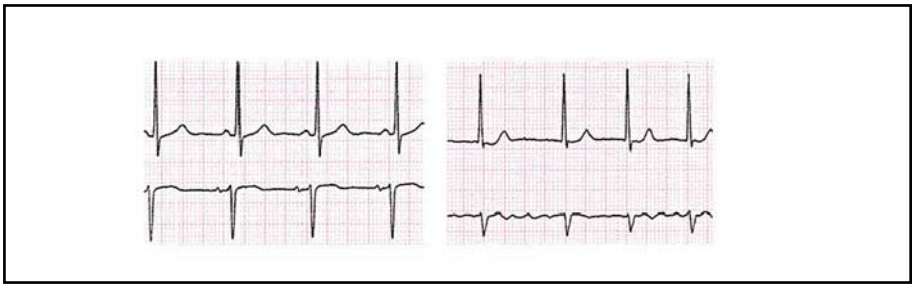

Figure 1: *ECG tracings showing normal sinus rhythm (left panel) and AF (right panel).*

Dr Diane Fatkin

common exposure of family members to environmental and lifestyle factors, these studies provided the first strong evidence that genetic factors might be involved in AF pathogenesis.

Atrial Fibrillation as a Complex Disease

Both inherited and acquired factors have been implicated in the aetiology of many common diseases. Although the role of genetics in AF has only recently begun to be investigated, it is anticipated that AF will also prove to be a complex disorder and that a spectrum of genetic defects of varying severity will be involved **(Figure 2)**. Families in which AF segregates as a Mendelian trait represent a minority of all cases. In these families, there is generally a single gene mutation that is sufficient to cause disease. Although genetic factors may be involved in patients of varying ages, monogenic inherited forms of AF should be sought particularly in young patients with lone AF and a positive family history. More commonly, especially in older individuals, there may be one or more genetic variants that alter disease susceptibility, together with acquired co-morbid conditions that predispose to AF. In this setting, there may be a positive family history but with a non-Mendelian inheritance pattern, or the family history may be negative. Elucidation of these genetic defects will require large, well-characterised populations of patients with AF as well as healthy control subjects. The development of single nucleotide polymorphism (SNP) arrays and HapMap data showing the genome-wide organization of SNPs into discrete clusters has provided powerful new tools for these genetic analyses. In the first major study of this type, Gudbjartsson and colleagues[11] reported a genome-wide case-control association analysis that was performed in 550 patients with AF and 4,476 control subjects. A single significant association was found with a set of SNPs located in chromosome 4q25. This finding was replicated in three separate Caucasian study populations and one Chinese study population. Interestingly, this set of SNPs was in a region of the genome that was remote from any known genes, and so a mechanistic explanation for a link with AF has yet to be determined. Identification of SNPs that can be used to predict susceptibility to AF, drug responsiveness and outcome will be a major focus of research over the next decade. Gene discovery in families with monogenic disease is a starting point for finding key genes for subsequent SNP association studies in cohorts of patients with more common complex forms of AF.

Gene Mutations in Familial Atrial Fibrillation

In order to identify those individuals in whom there may be a genetic basis for AF, a critical first step is to recognise familial disease and a detailed family history should be taken from all patients who have a new onset of AF, irrespective of the presence of concurrent risk factors. The medical history of the index case (proband) and first-degree family members may include AF and/or associated features such as thromboembolic events, heart failure, pacemaker insertion or sudden death.

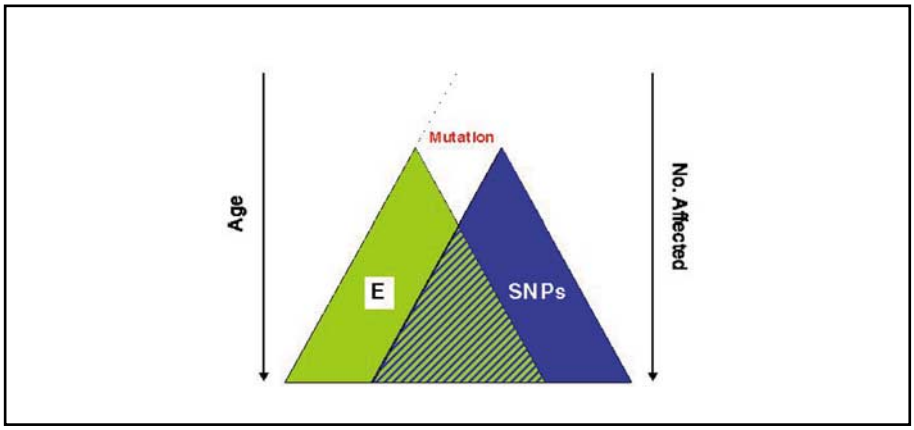

Figure 2: *AF "pyramid" showing predicted relative importance of genetic factors (single gene mutations and SNPs) and atrial environmental factors [E], such as atrial stretch, in patients of varying age with AF.*

ECG screening may reveal individuals who have asymptomatic AF or other changes, such as sinus bradycardia, atrioventicular conduction block, or short/long QT intervals. Echocardiography may show abnormalities of left atrial size or left ventricular size and function. Once the clinical status of family members is determined, a family pedigree can be drawn and evaluated for its inheritance characteristics. Autosomal dominant inheritance has been observed most commonly in families with adult-onset AF.

A number of different approaches can be used to identify disease-causing genes. In large families, DNA samples from all individuals can be included in a genome-wide linkage analysis. This will enable a chromosomal locus to be mapped in which there are polymorphic markers that link with disease in the family. A database search is then performed to select a short-list of candidate genes within the disease interval for subsequent evaluation. Mutation screening of candidate genes is performed using methods such as DNA sequence analysis. In small families that are unsuitable for linkage studies due to insufficient numbers, mutation screening of candidate genes is performed using DNA samples from the family probands. To be a candidate for AF, a gene is required to be expressed in the atrium and have functional properties that could foreseeably be involved in atrial arrhythmogenesis. Using these strategies, a number of chromosomal loci and disease genes for adult-onset familial AF have been found (reviewed in[12]). The majority of mutations have been located in genes that encode cardiac ion channels, particularly K+ ion channels and the Na+ ion channel. Very few mutations in each of these disease genes have been reported, however, and studies performed in cohorts of patients with familial and lone AF have demonstrated that mutations in these genes collectively account for a very small proportion of all AF cases. The genes that cause AF in the vast majority of families have yet to be determined.

Discovery of a Novel Stretch-Sensitive Mutation

Identification of disease-causing mutations in families with AF is a current focus of our research. These studies are performed jointly by a team of clinicians and scientists at the St Vincent's Hospitals, St Vincent's Clinic, and the Victor Chang Cardiac Research Institute. A large number of families with AF are participating in our studies and active recruitment is ongoing. We have recently performed mutation screening of genes encoding cardiac K+ ion channels in our patient cohort and have identified one novel missense mutation, R14C, in the *KCNQ1* gene in one family.[13] **(Figure 3)**. There was a high prevalence of hypertension amongst members of this family, with enlarged left atria observed in many of the individuals in the older generation. Hypertension and left atrial dilatation are both known to be independent risk factors for AF. We found, however, that AF developed only in those individuals who had hypertension, left atrial dilatation and the *KCNQ1* mutation **(Figure 4)**. The mutation was present in all individuals in the family who had AF and was not seen in any DNA samples from a large cohort of healthy volunteers. We evaluated the functional consequences of the *KCNQ1* mutation using electrophysiological studies in CHO cells. The *KCNQ1* gene encodes the a-subunit of the I_{Ks} channel that contributes to the repolarisation phase of the cardiac action potential. Patch-clamp studies of the normal and mutant *KCNQ1* showed no effect on I_{Ks} activation under baseline conditions. However, when cells were subjected to osmotic stress to mimic the effects of cell stretch, there was a marked increase in I_{Ks} current. When these data were included in a computer model of the human atrial action potential, it was predicted that the mutation would have a gain-of-function effect and shorten the action potential duration. These changes would predispose to the development of AF by a re-entrant arrhythmia mechanism.

Interactions Between Genetic Factors and Atrial Stretch

A unifying feature of the cardiac and systemic disorders that predispose to AF is the presence of atrial pressure and/or volume overload that results in increased wall stress and chamber dilatation. Atrial size increases with age,[14] as does the prevalence of these co-morbidities.[5] Atrial wall stretch has numerous short-term and long-term sequelae including altered activity of stretch-activated channels and intracellular Ca^{2+} concentration, release of local

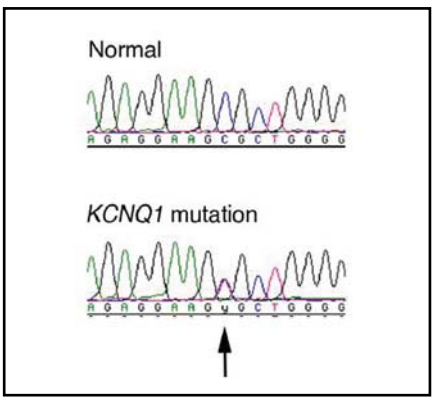

Figure 3: *DNA sequence traces showing normal KCNQ1 sequence and a KCNQ1 mutation (C to T substitution that results in a R14C amino acid change).*

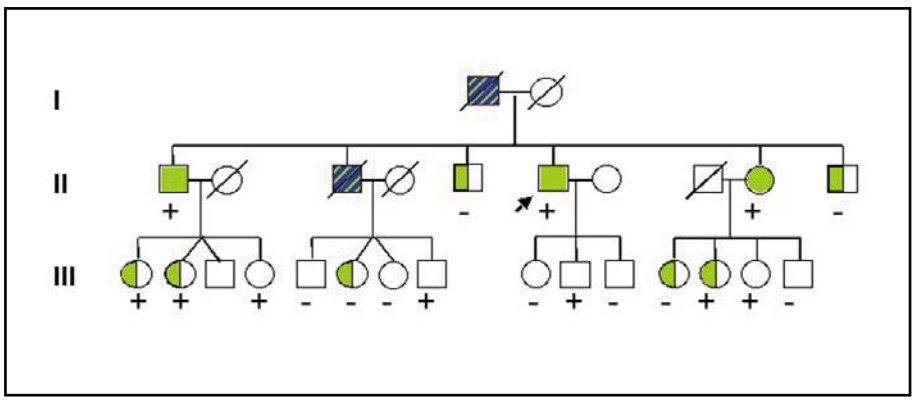

Figure 4: *Pedigree of a family with AF due to a stretch-sensitive KCNQ1 mutation. Males are denoted by squares, females by circles. Filled symbols indicate hypertension (left half) and AF (right half) or uncertain phenotype (diagonal lines). The family proband is indicated by an arrow. The presence (+) or absence (-) of the KCNQ1 mutation is indicated.*

neurohumoral factors, cell loss, fibrosis, ischaemia, oxidative damage, altered myofibrillar energetics, de-differentiation of cardiomyocytes and altered gene expression.[15] Collectively, these changes contribute to impaired atrial contractile function and further atrial dilatation. Atrial size has been shown to be an independent risk factor for AF[3] and sustained AF can result in electrical and structural remodelling of the atria and chamber dilatation.[15] There is strong evidence that atrial size is an important determinant of AF risk but not all individuals who have atrial dilatation develop AF. Our discovery of a stretch sensitive mutation in a family with AF suggested, for the first time, that interactions between an inherited ion channel mutation and atrial "environmental" factors might promote AF. These observations open up new avenues for genetics research and patient management. We suggest that in populations of individuals who have atrial dilatation due to conditions such as hypertension, the presence of stretch-sensitive SNPs might select a subgroup at increased risk of AF. The finding of stretch-sensitive genetic variants in families and in at-risk populations has significant clinical implications since aggressive therapy to modify the underlying cause of atrial dilatation may enable AF to be prevented.

Conclusions

There is increasing recognition that genetic factors may have a role in AF development and a family history should be taken in all patients with a new onset of AF. Studies of families in which AF results from a single inherited gene mutations provide a valuable resource for identifying the molecular defects that are involved in AF pathogenesis and participation in genetic research studies is encouraged. In patients without a well-defined family history, AF may result from the combined effects of one or more genetic factors that modify disease susceptibility as well as acquired factors. Elucidation of the interactions between genetic and acquired factors, such as atrial stretch, may not only enable selection of patients with an increased propensity for AF but also point to new strategies for prevention of AF.

Acknowledgments

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Dr Nigel Biggs

Trends in Management of Vestibular Schwannoma (Acoustic Neuroma)

Introduction

The management paradigm of vestibular schwannoma has changed significantly over the last two decades. The widespread availability of Magnetic Resonance Imaging (MRI) and its increased utilisation has resulted in an increased diagnosis of small tumours. The instance of such tumours is now thought to be closer to 1:80,000 per year.[1] The availability of high resolution scanning has also enabled many of these tumours to be tracked progressively over time and further information regarding the growth rate of such tumours is now available. As a consequence of this there has been a shift in the policy of treating all diagnosed tumours. The increased usage of stereotactic radiotherapy (radiosurgery is a misnomer) has also altered therapeutic choices to both patients and clinicians. As patients are becoming more informed about these choices the decision making process has become more complex.

There is also little doubt that treatment outcomes are better in the units with a large experience such as St Vincent's. The otolaryngology and skull base unit led by Professor Paul Fagan has experience of managing over 1200 vestibular schwannomas and other cerebellopontine angle (CPA) tumours.

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Vestibular Schwannoma – Growth And Diagnosis

The natural history of vestibular schwannoma remains unpredictable. Although there has been research looking at markers of growth, there have been no consistent findings. The average growth rate is quoted as 1mm to 2mm per year; however widespread experience demonstrates a broad range of growth rates between no growth and several millimetres per year.

Vestibular schwannoma is increasingly detected when small due to the availability of MRI scanning and a higher index of suspicion on behalf of otolaryngologists. Any adult presenting with a unilateral or asymmetric sensorineural hearing loss of greater than 10 decibels in two or more frequencies is recommended to have their cerebellopontine angle imaged. The most cost effective form of imaging is a non-contrast MRI scan of the internal auditory canal (IAC) with fine slices through the area. A mass detected on T2 weighted images is then usually followed up with contrasted films. Auditory brainstem evoked responses and contrasted CT scanning of the area is now only used where MR imaging is not possible.

Management can be divided into three main areas: non-surgical treatment (observation), stereotactic radiotherapy and surgery. The clinical decision making for treatment is based on a number of factors including the status of hearing, vestibular function, presence or absence of other cranial nerve deficits and co-morbidity. The most important

factors still remain the size and location of the tumour. The size of the tumour refers to the measured diameter within the cerebellopontine angle.

Large Vestibular Schwannoma

Large tumours are generally described as those greater than 3cm in diameter in the CPA **(Figure 1).** Patients presenting with tumours of this size often have symptoms of hearing loss, tinnitus and some vestibular function. The degree of this may vary according to the position of the tumour in relation to the cochlear vestibular nerve. More medially based tumours may present with only a minor hearing loss, and rarely very large tumours can present with virtually normal hearing. Conversely, quite small tumours when presenting in the lateral aspect of the IAC often demonstrate early symptoms and signs. In general, tumours of greater than 3cm are compressing the brainstem and forcing the facial nerve to take a more extended course to the internal auditory meati. The facial nerve is therefore at greater risk. Increased brainstem compression over time as the tumour grows often results in ataxia and compression of the 4th ventricle which may lead to hydrocephalus.

Most national and international centres which manage vestibular schwannoma recommend surgery for large tumours. It is more difficult to control large tumours with radiotherapy and there is concern over initial radiation induced swelling of the tumour, which may precipitate hydrocephalus after commencement of treatment **(Figure 2)**. The goal of surgery for tumours of this size is removal of the tumour with preservation of adjacent cranial nerves. Hearing preservation in tumours of this size is very unlikely and efforts should be concentrated on preservation of facial nerve function. Surgical approaches for tumours of this size are usually translabyrinthine or retrosigmoid. The advantages and disadvantages of each approach and utilisation of approach varies from unit to unit. The translabyrinthine approach is the most commonly used approach at St Vincent's Hospital and provides the best outcomes. The primary advantages of this approach is that the facial nerve can be readily identified at the lateral end of the internal auditory canal, there is a shorter distance between surgeon and the tumour compared to the retrosigmoid approach. Finally, there is little or no compression of the cerebellum required in exposing the tumour.The advantage of the retrosigmoid approach is a wider view of the CPA and particularly the inferior aspects along with the lower cranial nerves.

The aim of surgery is tumour removal and it is rare that an elective sub-total dissection would be performed. Tumour removal however is not performed at the cost of sacrificing the facial nerve. In situations where a small fragment of 1mm to 2mm in size is left firmly adherent to the facial nerve, it is felt that sacrificing the facial nerve to remove this residual tumour is not necessary. Long term follow up of these patients rarely demonstrates any recurrence of tumour. Subtotal removals where a larger volume of tumour is left and the blood supply not removed however, can lead to significant recurrence. As surgery for very large tumours can be quite lengthy, in some circumstances a two stage approach is undertaken where the translabyrinthine bone removal is performed days prior to tumour resection. Facial nerve outcome is usually dictated by the experience of the surgical team and the size of the tumour. Tumours in excess of 3cm in diameter have significantly poorer facial nerve outcomes than smaller tumours (House – Brackmann grades 3-6). With larger lesions there is also an increased risk of post operative complications such

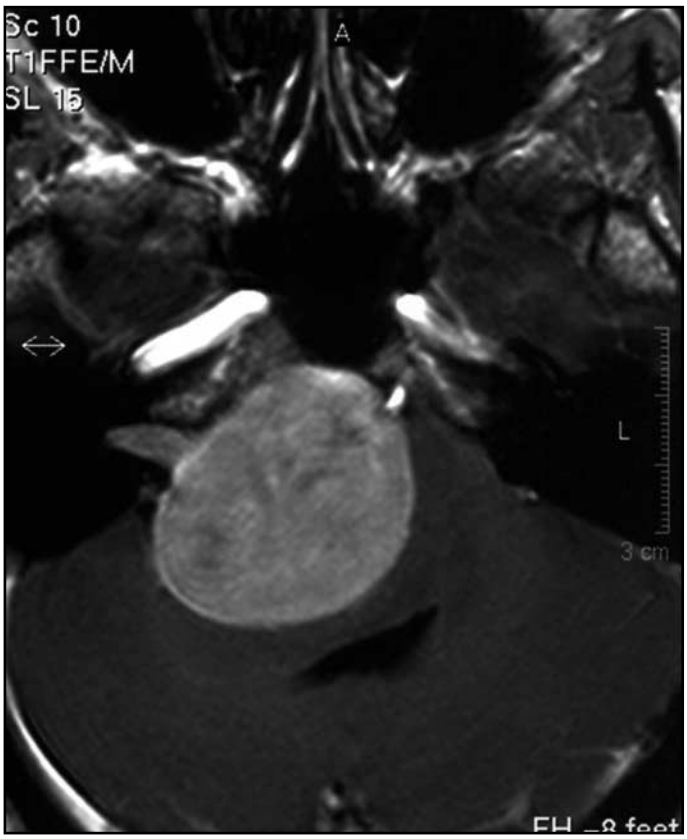

Figure 1. *T1 weighted axial MR scan with contrast of the CPA demonstrating a very large right vestibular schwannoma with significant brainstem distortion.*

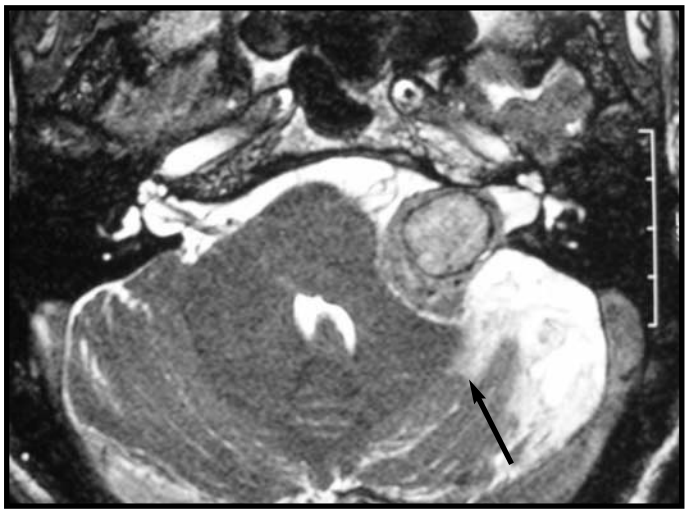

Figure 2. *T2 weighted axial MR scan of a patient having had previous retrosigmoid approach and subtotal vestibular schwannoma removal followed by Gamma Knife stereotactic radiotherapy. Note the centrally demarcated irradiated area with the surrounding margin of growing tumour (arrow).*

as stroke, other cranial nerve palsies or secondary hydrocephalus. Fortunately, the instance of such complications if very low.

Medium Vestibular Schwannoma

These are usually classified as tumours of 1cm to 3cm within the cerebellopontine angle **(Figure 3)**. The decision making process for tumours of this size is often determined by the size and position of the tumour. Tumours 2cm or larger are contacting the brainstem and are therefore more likely to require treatment, whereas tumours closer to 1cm in size, where there is still CSF visible between the tumour and the brainstem, may be managed more conservatively. Other patient related factors and, in particular, hearing is always considered in these cases. The degree of pre-existing hearing loss, age and general health of the patient is considered. Elderly patients with tumours of this size tend to be managed more conservatively when compared to young patients who are more likely to require treatment in the long term.

Surgical outcomes when managing tumours of this size are often compared to those of radiotherapy. Facial nerve preservation rates of tumours of this size at St Vincent's Hospital is over 95 percent. There is, however, argument that facial nerve preservation rates with radiotherapy are as high as 98 percent.[2] Furthermore, with radiotherapy in a percentage of these cases auditory function is preserved. Trigeminal neuralgia however remains a problem for this modality with more than five percent of patients reporting this post-treatment.[3] Trigeminal neuralgia following microsurgical resection for tumours of this size is less than one percent in our experience. More controversial is the risk of malignancy following radiotherapy. While it is accepted that in the elderly this risk is not relevant, radiotherapy in a patient in their fourth or fifth decade does carry a long term risk. With increasing use of radiotherapy, more reports are being published on malignant transformation or malignancy within the radiation field. There have been at least 20 reports in the recent literature and more are expected.[4]

Small Vestibular Schwannoma

For intracanalicular tumours and tumours with minimal extent in the CPA (<1cm diameter) there has been the greatest change in management strategies. Historically theses tumours were always treated due to the concern of tumour growth over time. The role of surgery in these tumours focused often on hearing preservation procedures. Hearing preservation is considered where "useful" hearing is present which is classified as Class A **(Table 1)**. Middle cranial fossa or retrosigmoid approaches to the CPA are used where an attempt at hearing preservation is made. The middle fossa approach has the advantage of being able to deal with lateral intracanalicular tumours whereas the retrosigmoid approach is more suited to those medially positioned. The middle fossa approach however is quite technically challenging and does increase the risk of facial nerve injury. As a broad rule, any approach to save the cochlear component of the auditory nerve does increase the risk of facial nerve injury or residual unresected tumour. Hearing preservation rates (Class A or B) for small and intracanalicular tumours vary between 50 and 70 percent.[5]

The use of radiotherapy for these small tumours has become more

Table 1: *AAOHNS classification of hearing 1995*

Class	PTA	SD
A	<30 dB	>70%
B	>30 dB <50dB	>50%
C	>50dB	>50%
D	Any	<70%

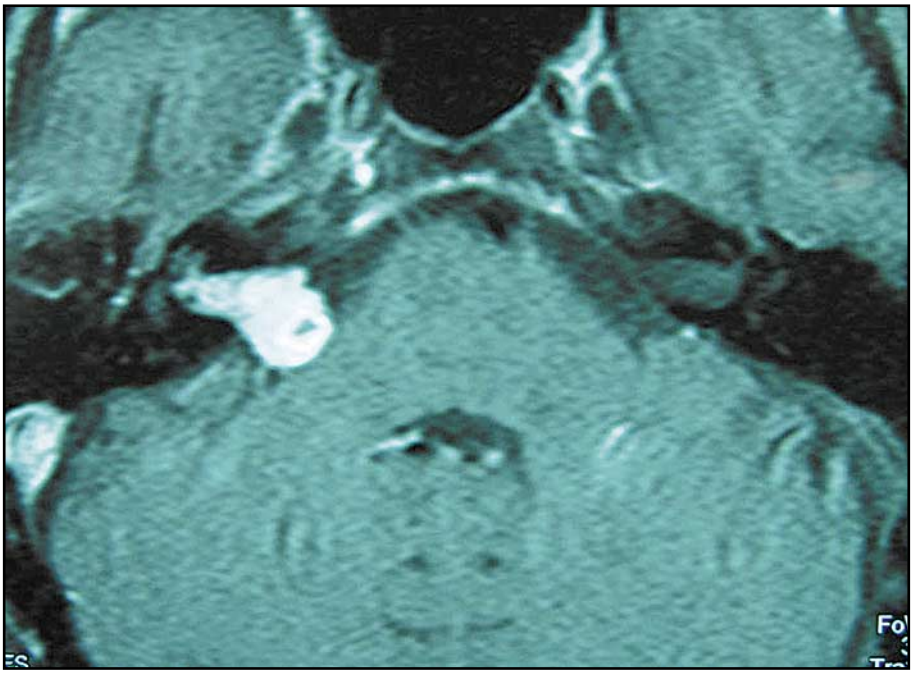

Figure 3. *T1 weighted axial MR scan with contrast of the CPA demonstrating a medium sized right vestibular schwannoma*

widespread with excellent tumour control rates and better hearing results.[6,7] As previously mentioned, there is the long term risk of induction of malignancy within the radiation field.

More recently there has been a shift towards conservative management of such tumours with the so called "watch and wait" approach. Long term studies in large numbers of patients managed this way have demonstrated a large proportion of these tumours grow so slowly that they often never require treatment or treatment can be delayed by many years.[8] Furthermore, many of these patients preserve their hearing so that when compared to the results of radiotherapy for tumours of this size it is difficult to see the benefits of any intervention.[9] This is also backed up by quality of life studies in this area. Patients who undergo any form of treatment always demonstrate deterioration in quality of life compared to the conservatively managed group.[10] The good outcomes associated with a watch and wait approach have impacted on the role of early surgical intervention.

Current policy for these tumours is to watch and wait where there is any functional hearing in patients of any age group and in the elderly this approach is usually adopted irrespective of degree of hearing loss. Based on this approach, the indications for intervention become: evidence of rapid growth on serial MR imaging, disabling imbalance, vertigo or strong patient desire for treatment due to the presence of an intracranial tumour. To try to detect those patients requiring intervention, a scanning regime of first repeating the scan at six months and then yearly scans is adopted. Those patients requiring treatment then undergo definitive translabyrinthine excision to maximise facial nerve preservation and minimise risk of residual disease.

Conclusion

There has been a significant shift in the management of vestibular schwannoma. A more conservative watch and wait policy for small to medium tumours has raised questions over the role of early intervention hearing preservation procedures and stereotactic radiotherapy. Surgery remains the modality of choice for medium to large tumours with radiotherapy reserved for the elderly or medically infirm.

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2008 St Vincent's Clinic Foundation Grants

The Ladies' Committee Sr Mary Bernice Research Grant – $100 000
St Vincent's Clinical School – ***Prof Terence Campbell***
"The state dependence of drug binding to the human-ether-a-go-go related gene K+ channel"

Adult Stem Cell Research – $100 000
Victor Chang Cardiac Research Institute – ***Prof Robert Graham***
"G-CSF in Angina patients with ischaemic heart disease to stimulate neovascularisation-GAIN II"

The Tancred Research Grant – $50 000
Garvan Institute of Medical Research – ***Dr Jerry Greenfield***
"Defining the insulin-signalling defect in human insulin resistance and type 2 diabetes"

The K & A Collins Cancer Research Grant – $50 000
St Vincent's Hospital – ***Dr Michael Buckland***
"Epigenetic changes in human brain tumours"

The Di Boyd Cancer Research Grant – $25 000
St Vincent's Hospital – ***Dr David Brown***
"Macrophage inhibitory cytokine-1: a potential screening test for colonic polyps"

The Froulop Vascular Research Grant – $40 000
St Vincent's Hospital – ***Dr Alan Farnsworth***
"Left atrial reduction for chronic atrial fibrillation and enlarged left atrium associated with mitral valve disease: long-term echo- and electro- cardiographic results"

Annual Awards –

- St Vincent's Hospital – ***Assoc Prof Debbie Marriott*** **($35 000)**
  "The prospective surveillance of invasive fungal infections in Australian Intensive Care Units"
- St Vincent's Hospital ***Prof Bruce Brew*** **($25 000)**
  "The kynurenine pathway of tyrptophan metabolism influences adult stem cell proliferation and differentiation"
- St Vincent's Hospital ***Prof David Ma*** **($25 000)**
  "Identification of diagnostic and prognostic indicators in acute myeloid leukaemia with normal karyotype by microRNA expression"
- St Vincent's Hospital ***Dr John Moore*** **($25 000)**
  "The role of Protein Kinase C epsilon in philadephia positive acute leukaemia and its affect during glivec treatment"
- St Vincent's Hospital – ***Assoc Prof Nicholas Pocock*** **($25 000)**
  "Dual Time Point 18F-FDG PET for the Evaluation of Suspected Malignancy"
- Victor Chang Cardiac Research Institute – ***Dr Catherine Suter*** **($25 000)**
  "Small RNA species and cancer development"

Travelling Scholarship – $10 000
The Committee recommended that 4 Travelling Scholarships each of $10 000 are awarded:

Department of Otolaryngology/Head and Neck Surgery – ***Dr Richard Harvey***
Rhinology/Endoscopic skull base fellowship ay the Medical University of South Carolina, South Carolina, USA

Department of Colorectal Surgery – ***Dr Rohan Ghett***
Clinical Observer Mount Sinnai Hospital Toronto and Clinical Observer Leeds General infirmary

Department of Cardiology – ***Dr Joseph Suttie***
DPhil in Cardiovascular Medicine at Oxford University – "Cardiac Magnetic Resonance Imaging in Hypertrophic Cardiomyopathy"

Heart Transplant Program – ***Dr Andrew Jabbour***
Collaborative research at Zensun Science and Technology Laboratory and Fudan-Zensun Cellular Signalling Research laboratory, School of Life Science, Fudan University, Shanghai, China

Multi-disciplinary Patient Focussed Research Grants

St Vincent's Private Hospital – $25 000 – *Prof Kim Walker*
"A Multidisciplinary Model of Care to Improve Warfarin Anticoagulation"

St Vincent's Hospital – $25 000 – *Ms. Serena Knowles*
"Multi-disciplinary implementation of an evidence-based practice: Collaborative quality improvement in Intensive Care Unit (ICU) patient care"

St Vincent's Hospital – $25 000 – *Ms Valerie Bramagh & Ms. Nicky Sygall*
"Stroke Education and Support Program -Community follow- up for patients of Acute Stroke Care Unit (ASCU)"

Dr Edwin Szeto

Radioimmunotherapy for Non-Hodgkin's Lymphoma

Introduction

Radioimmunotherapy (RIT) is defined as a treatment modality in which cytotoxic radiation is delivered to tumour cells via target-specific antibodies.[1] Radiolabelled monoclonal antibodies targeting the CD20 antigen in B-cell lymphoma has demonstrated efficacy and safety. How to best use these agents in different clinical settings remains uncertain.

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Background

Non-Hodgkin's lymphoma (NHL) is the fifth most common malignancy in both Australia and the USA and ranks sixth in cancer mortality. Eighty five per cent of NHLs are B-cell lymphomas. Most cases fall into two histological subtypes, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL). FL is the second most common type of NHL comprising 35 per cent to 40 per cent of all adult lymphomas. The term "indolent" lymphoma is often used to describe FL (and a number of other less common histological forms) due to the slow clinical course with a long median survival of eight to 10 years. While patients might initially respond to therapy, the disease is punctuated by multiple episodes of recurrence (with progressively lower response rates and shorter duration of response after each additional treatment) leading ultimately to death due to refractory disease, transformation to an aggressive large B-cell pathology or complications of therapy.[2, 3]

Immunotherapy

Rituximab is a chimeric anti-CD20 monoclonal antibody which targets the CD20 antigen which is present on the surface of mature B-cells and on the neoplastic cells of approximately 93 per cent of patients with B-cell malignancies such as NHL. The CD20 antigen is not present on stem cells, pro B-cells, plasma

cells or other non-lymphoid tissues.[4] Furthermore, this antigen does not circulate in the plasma as free protein and is not shed into the circulation after antibody binding, so that there is very little free antigen that would block antibody delivery to sites of disease.[5]

The results of randomised phase III trials indicate that the addition of Rituximab to combination chemotherapy prolongs progression-free and overall survival compared to chemotherapy alone.[6]

In Australia, TGA approved Rituximab immunotherapy is available to patients with NHL for the following indications:

1. CD20 positive, relapsed or refractory low grade or follicular, B-cell NHL.
2. CD20 positive, previously untreated diffuse large B-cell NHL, in combination with chemotherapy.
3. CD20 positive, previously untreated Stage III/IV follicular, B-cell NHL, in combination with chemotherapy.

There are ongoing trials to determine the role of Rituximab as frontline treatment in asymptomatic patients with low tumour burden and its role as maintenance therapy versus observation/retreatment.

However, all tumour cells may not be bound by monoclonal antibodies and might be resistant to its anti-tumour and immune activating mechanisms. A substantial number of patients with indolent lymphomas do not respond to Rituximab.[7]

RADIOIMMUNOTHERAPY

In an attempt to augment the effectiveness of antibody preparations, radioisotopes, toxins and other molecules have been attached to antibodies. B-cell lymphoma is a particularly good candidate for RIT because the disease is inherently radiosensitive, and the malignant cells in the blood, bone marrow, spleen and lymph nodes are accessible to monoclonal antibodies. Furthermore, even if a tumour is bulky or portions lack CD20 expression, the nearby targeted radiation will cause cytotoxicity (the so-called "bystander" effect) while limiting undesirable non-specific radiation.[8]

RIT in refractory/relapsed indolent NHL

RIT has been proven to be so effective that the USA Food and Drug Administration approved the first ever radioimmunoconjugate for the treatment of a malignancy in February 2002, when ^{90}Yttrium-Ibritumomab (Zevalin) was licensed for the treatment of indolent or transformed, relapsed or refractory B-cell lymphoma. Subsequently, ^{131}Iodine-Tositumomab (Bexxar) was also approved for indolent or transformed B-cell NHL relapsed or refractory after Rituximab.[9] The approved indication for Zevalin in Europe involves patients with follicular lymphoma who have relapsed or are refractory after prior Rituximab-containing treatments. Both of these radiolabelled anti-CD20 monoclonal antibodies are deliberately mouse antibodies in order to accelerate antibody clearance and limit the effects of prolonged total body irradiation. [10] **Table 1** summarises the main physical characteristics of these two products.

When comparing the results of RIT with the single agent Rituximab in heavily pre-treated patients, RIT confers a better or similar response rate with the convenience of single-dose administration.[11]

Table 2 summarises the pivotal clinical trials involving RIT for the approved clinical setting of refractory/relapsed indolent lymphomas.[12-20] The results for ^{90}Y-Ibritumomab and ^{131}I-Tositumomab are similar. Yttrium-90 is a pure beta β-emitter; the long path-length of its β particles (5.0mm) is advantageous in tumours with a heterogeneous or low distribution of CD20 antigen and is potentially more efficacious against a larger tumour mass.[1, 21] In addition, being a pure β-emitter, patients treated with Yttrium-90 do not require hospitalisation. Iodine-131 is a beta and gamma (γ) emitter, and the path-length of its β particles is shorter than that of Yttrium-90; therefore it has been suggested to be better suited for therapy in minimal residual disease.[22] However, there is a wealth of knowledge and experience with the use of Iodine-131 in other clinical settings (notably in thyroid cancer treatment). This, together with its low cost, availability and the ability to harness its γ emissions for imaging purposes are particularly advantageous (imaging allows patient specific therapeutic dose calculations based on bioclearance curves and isotope retention times). Due to its γ emissions, patients receiving Iodine-131 require hospitalisation to reduce radiation exposure to healthcare workers and the patient's family.

	^{131}Iodine-Tositumomab	^{90}Yttrium-Ibritumomab
Linker	None	Tiuxetan
Isotope decay	Beta & gamma	Beta
Half-life	8.0 days	2.7 days
Path-length	0.8 mm	5.0 mm
Energy	0.61 MeV	2.3 MeV
Non-tumour distribution	Thyroid	Bone
Imaging	Possible	Not Possible

Table 1

St Vincent's Hospital Experience

St Vincent's Hospital Sydney was a participant in the Phase II Multicentre Australian Trial of ^{131}I-Rituximab RIT in relapsed or refractory indolent NHL.[20] Following closure of the trial on 31 December 2004 and the analysis of the excellent outcomes, with objective overall response rate (ORR) of 76 per cent and complete response (CR) of 53 per cent, ^{131}I-Rituximab is available via the TGA's Special Access Scheme only in the institutions that participated in the trial (St Vincent's Hospital is the only hospital in NSW). The trial criteria for patient selection were all patients with relapsed or refractory NHL who qualify for TGA approved Rituximab immunotherapy, and ^{131}I-Rituximab remains available "free" to patients who satisfy this criteria. The radioimmuno-conjugate produced in the sterile facilities of the Nuclear Medicine department at St Vincent's Hospital is the equivalent of ^{131}I-Tositumomab. Although ^{90}Y-Ibritumomab may be purchased and used in Australia, the cost is $25,000 per patient per treatment.

Safety

The efficacies of RIT are achieved with minimal toxicity. The toxicity profile of these RIT agents has become firmly established by the trials listed in **Table 2**. The Australian trial demonstrated toxicity was principally hematologic, with grade 4 thrombocytopenia occurring in four per cent and grade 4 neutropenia in 16 per cent of patients. The median time to platelet nadir was six weeks, seven weeks for neutrophils and eight weeks for hemoglobin. No patient was hospitalised with infection.[20] Factors predicting for hematological toxicity include the presence of bone marrow involvement and the number of previous therapies. Non-hematological toxicity (asthenia, nausea and chills) is typically mild.[23, 24]

Human anti-mouse antibody (HAMA) may develop but is rare. No adverse event associated with the development of HAMA has been reported. Furthermore, the development of HAMA does not appear to compromise response to therapy.[16]

There has been some concern that systemic exposure to radiation may result in an increased frequency of myelodysplastic syndrome or acute myeloid leukaemia following RIT. Reviews have shown that the incidences are in line with the expected frequency based on patients' prior chemotherapy.[25]

Novel Concepts of Radioimmunotherapy

A. RIT retreatment

There is evolving evidence that patients treated with RIT can be safely and effectively retreated in certain situations. Kaminski et al.[17] demonstrated ORR of 56 per cent in patients retreated with ^{131}I-Tositumomab (CR 25 per cent). Interestingly overall duration of response in those achieving CR was actually longer than seen with initial therapy (35 months vs. 14.5 months). There was no variable that predicted response to retreatment or duration of response. Further study is required.

B. RIT as frontline therapy

Table 3 summarises several trials using RIT as frontline treatment for indolent NHL. In all these studies, patients achieved very high ORR (75 per cent – 95 per cent) with minimal toxicities.[26-29] The study reporting the highest ORR and CR (95 per cent and 75 per cent respectively) was the only study evaluating RIT as a single agent in patients with previously untreated Stage III/IV follicular lymphoma.[28] It is noted that the Australian TGA has approved Rituximab immunotherapy for this indication. Radiolabelled Rituximab would theoretically augment the responses achieved with Rituximab alone. Further studies are required to evaluate this regimen and others.

C. RIT in aggressive histologies

Indolent lymphoma sometimes transforms into a diffuse aggressive

Reference	Study phase	RIT used	Patients	Responses	DOR (months)	TTP (months)
Vose et al. 2000 (12)	II multicentre	^{131}I-Tositumomab	47	Low grade ORR 57% CR 27% Transformed ORR 60% CR 50%	9.9 median 8.2 low grade 12.1 transformed	NR
Witzig et al. 2002 (13)	I, II	^{90}Y-Ibritumomab	57	ORR 74% CR 15%	5.4	6.8 median
Wiseman et al. 2002 (14)	II	^{90}Y-Ibritumomab	30	ORR 83% CR 37%	11.7 median	9.8 median
Witzig et al. 2002 (15)	III	^{90}Y-Ibritumomab ^{131}I-Tositumomab	143	^{90}Y: ORR 80%; CR 30% ^{131}I: ORR 56%; CR 16% (p=0.04)	^{90}Y 64% ≥ 6/12 ^{131}I 47% ≥ 6/12 (p=0.03)	^{90}Y 11.2 ^{131}I 10.1 (p=0.173)
Davies et al. 2004 (16)	II	^{131}I-Tositumomab	41	ORR 76% CR 37%	Overall 1.3 yrs Those achieving CR 3.4 yrs	NR
Kaminski et al. 2005 (17)	II multicentre	^{131}I-Tositumomab	32	ORR 56% CR 25%	15.2 for responders	NR
Wiseman & Witzig 2005 (18)	Retrospective	^{90}Y-Ibritumomab	211	Long-term response 37%	28.1 median	29.3 median 53.9 for ongoing responders
Fisher et al. 2005 (19)	Integrated analysis of 5 clinical trials	^{131}ITositumomab	250	ORR 47-68% CR 20-38%	45.8 median for long-term responders	32% 12 months
Leahy et al. 2006 (20)	II multicentre	^{131}I-Tositumomab	91	ORR 76% CR 53%	20 for CR 7 for PR	13

ORR: overall response; CR: complete response; PR: partial response; DOR: duration of response; TTP: time to progression; NR: not reported

Table 2: RIT for the treatment of refractory/relapsed indolent lymphomas

histology which responds poorly to standard chemotherapy and has a median survival of less than two years. The only modality shown to improve outcomes in this setting is allogenic or autologous stem cell transplant.[8] There is an obvious need for improved treatment modalities.

Mantle cell lymphoma combines the chemoresistant properties of indolent lymphoma with a more aggressive clinical pattern.

Table 4 summarises several trials reporting the use of RIT in the above settings.[30-34] In Mantle cell lymphoma, the results suggest a significant benefit for the addition of RIT to standard chemotherapy. The favourable results in diffuse large B-cell lymphoma (DLBCL) has led several groups to evaluate RIT as consolidation after standard chemotherapy and Rituximab. In 2006, the TGA in Australia approved the use of Rituximab in DLBCL in combination with chemotherapy. Radiolabelled Rituximab should theoretically augment the efficacy of Rituximab alone.

D. RIT in hemopoietic cell transplantation

High dose chemotherapy followed by autologous hemopoietic cell transplantation (AHCT) has been shown to be superior to conventional salvage chemotherapy in patients with relapsed aggressive NHL and is potentially curative.[35] The role of AHCT in indolent NHL is promising but remains investigational.

The potential to re-infuse malignant lymphoid cells with the stem cell graft is an important concern with AHCT. Immunotherapy with antibodies directed against lymphoid cells has been incorporated into transplantation strategies with the aim of eliminating malignant cells from the graft, and Rituximab has emerged as an important agent for this purpose. Total body irradiation (TBI) has been used as part of some strategies for AHCT due to the radiosensitivity of NHL cells, but its use has been limited due to significant toxicities. RIT represents an alternative treatment modality that combines the specificity of monoclonal antibodies and the efficacy of radiation.

Table 5 summarises the key trials using RIT in stem cell transplantation conditioning.[36-47] The field of stem cell transplantation allows the exploration of higher than standard doses of RIT, since myelosuppression ceases to be the dose-limiting toxicity. In these studies, there have been no reports of adverse effects on stem cell engraftment and the recovery from treatment induced aplasia. All study designs allow a minimum of 14 days between administration of RIT and the infusion of stem cells.

The use of RIT does not appear to increase other organ toxicity.[9] Overall,

Reference	Study phase	RIT used	Patients	Responses
Press et al. 2003 (23)	II: CHOP (6 cycles) followed by ^{131}I-Tositumomab	^{131}I-Tositumomab	90	ORR 90%; CR 67%
De Monaco et al. 2005 (27)	II: CHOP-Rituximab (3 cycles) followed by ^{90}Y-Ibritumomab-Rituximab	^{90}Y-Ibritumomab	8	After CHOP-Rituximab: ORR 75%; CR 25% After ^{90}Y-Ibritumomab-Rituximab: CR 87.5%
Kaminski et al. 2005 (28)	II	^{131}I-Tositumomab	76	ORR 95%; CR 75% 5 year OS: 89%
Leonard et al. 2005 (29)	II: Fludarabine (3 cycles) followed by ^{131}I-Tositumomab	^{131}I-Tositumomab	35	After Fludarabine: ORR 89%; CR 3 patients After ^{131}I-Tositumomab: ORR 100%; CR 30 patients

ORR: overall response rate; CR: complete response; OS: overall survival

Table 3: RIT as frontline treatment of Indolent Lymphoma

Reference	Histology	RIT used	Patients	Responses
Zelenetz et al. 2002 (30)	Diffuse lage cell	^{131}I-Tositumomab	71	ORR 39%; CR 25%
Morschhauser et al (2004 (31)	Diffuse large cell	^{90}Y-Ibritumomab		ORR 44%
Younes et al 2005 (32)	Mantle cell	^{90}Y-Ibritumomab	22	ORR 36%; CR 14%
Smith et al. 2006 (33)	Mantle cell	^{90}Y-Ibritumomab	56	CHOP + Rituximab: ORR 72%; CR 14% CHOP + Rituximab + ^{90}Y-Ibritumomab: ORR 84%; CR 45%
Jurczak et al. 2006 (34)	Mantle cell	^{90}Y-Ibritumomab	29	CR 75% overall CR 95% in previously untreated patients

Table 4: RIT in aggressive histologies

high-dose RIT appears to be efficacious and safe for conditioning prior to AHCT in patients with relapsed or refractory NHL, with improved overall survival and progression-free survival.

Conclusion

RIT has added significantly to the therapeutic armamentarium in B-cell NHL treatment. RIT has the advantage of a short administration time with acceptable toxicity. It is currently available in Australia for CD20 positive, relapsed or refractory low grade or follicular B-cell lymphoma. As more experience is acquired with the use of RIT, there will likely be a shift towards earlier administration in the disease course, as well as in combination with chemotherapy and in the myeloablative setting, both in indolent lymphoma and in other lymphoma subtypes.

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Reference	Study phase	RIT used	Patients	Responses	Follow-up	Overall survival	PFS
Press et al. 1993 (36)	I	^{131}I-Rituximab	43	ORR 95%; CR 84%	26 months	> 21 months	>11 months
Liu et al. 1998 (37)	I, II	^{131}I-Rituximab	29	ORR 86%; CR 79%	42 months	68%	42%
Press et al. 2000 (38)	I, II	^{131}I-Tositumomab + cytoxan & VP-16	52	89% disease-free state	2 years	83%	68%
Gopal et al. 2002 (39)	I, II	^{131}I-Tositumomab + cytoxan & VP-16	16	ORR 82%; CR 73%	3 years	93%	61%
Gopal et al 2003 (40)	Non-randomised	^{131}I-Tositumomab & HDCT vs HDCT & TBI	27	^{131}I: ORR 93%; CR 85% TBI: NR	5 years	^{131}I: 67% TBI: 53%	^{131}I: 48% TBI: 29%
Winter et al. 2004 (41)	I, II	^{90}Y-Ibritumomab + BEAM	22	NR	3 years	60%	47%
Devizzi et al. 2005 (42)	II	^{90}Y-Ibritumomab	13	NR	6 months	84%	76%
Krishnan et al. 2005 (43)	II	^{90}Y-Ibritumomab + BEAM	24	NR	13 months	94%	74%
Nademanee et al. 2005 (44)	I, II	^{90}Y-Ibritumomab + Etoposide + Cyclophosphamide	31	NR	22 months	92%	78%
Shimoni et al. 2005 (45)	II	^{90}Y-Ibritumomab + BEAM autograft or Fludarabine allograft	16	ORR 100%; CR 87%	12 months	63%	44%
Vanazzi et al. 2005 (46)	I, II	^{90}Y-Ibritumomab	12	ORR 50%; CR 41%	8-12 months	NR	NR
Vose et al. 2005 (47)	I	^{131}I-Tositumomab + BEAM	23	ORR 65%; CR 57%	38 months	55%	39%

ORR: overall response; CR: complete response; PFS: progression free survival; TBI: total body irradiation; NR: not reported

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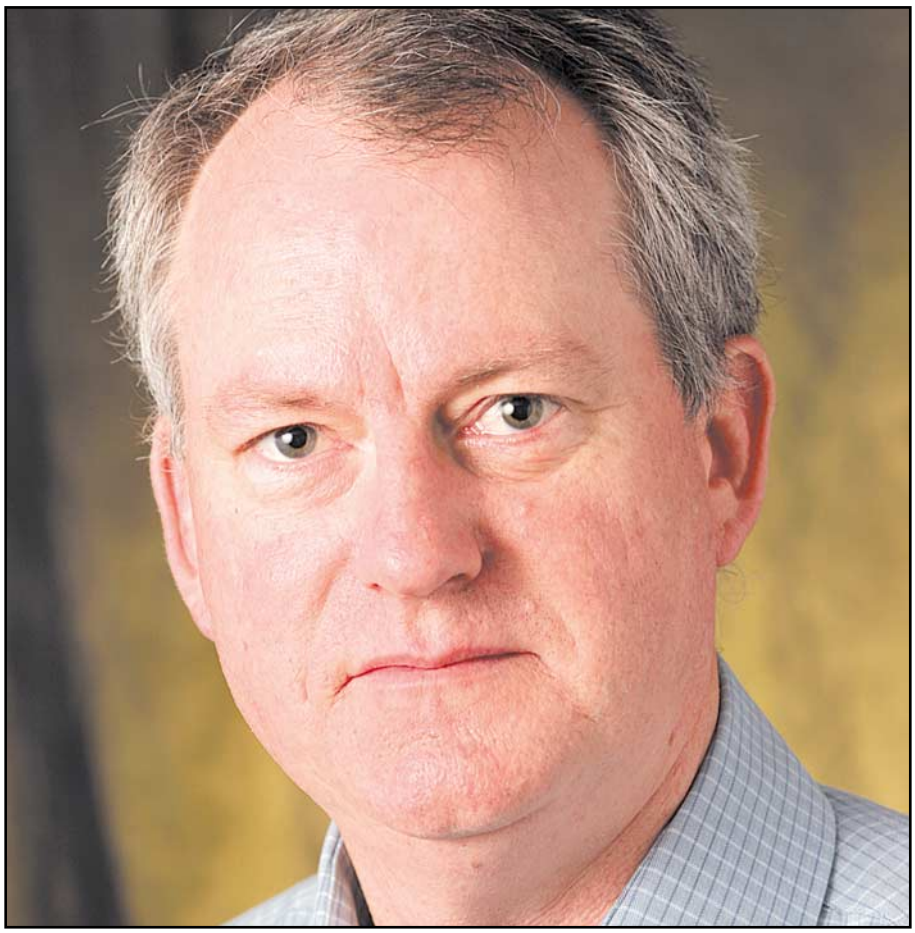
Dr Andrew S. Field

Teaching Fine Needle Aspiration Biopsy Cytology in Western, Central and Eastern Africa: an initiative based at St Vincent's Hospital



Fine needle aspiration biopsy (FNAB) is the technique of using a very small 23 to 25 gauge needle to puncture the skin to obtain material from palpable lumps, most commonly in the breast, thyroid and lymph nodes, and to sample deeper lesions in the lungs, abdomen and liver using ultrasound or CT guidance. For palpable lesions the FNAB can be carried out in clinics or doctors rooms and no local anaesthetic is required, although it can be used. The needle can be introduced simply by itself held between the fingers or attached to a syringe held in a holder which allows aspiration while holding the lesion firmly with the other hand. The FNAB technique was developed mainly in Scandinavia in the late 1950s and was pioneered in Australia by Professor Svante Orell, a Swedish cytopathologist of international fame, who trained at the Karolinska Hospital in Stockholm and then emigrated to Australia to work in Perth, Newcastle and finally Adelaide.

In the St Vincent's setting, we perform FNAB on palpable sites and radiologists carry out the biopsies of deeper sites. The fine needle aspiration material is used to make both air dried Giemsa stained and alcohol fixed Papanicolaou stained cytology slides and then the material can be used in a wide range of ancillary testing appropriate to the organ site, including the preparation of histological cell blocks for immunoperoxidase studies, flow cytometry, molecular studies,

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cytogenetics, cultures and electron microscopy.

In a setting where there are limited medical resources, such as large parts of sub-Saharan Africa, Asia and Central and Southern America, the FNAB technique is a powerful diagnostic tool since it requires very little infrastructure and equipment.[1] The challenge is to train cytopathologists in these countries to perform the FNAB and report the cytopathology.

In September 2006 I delivered a lecture on the role of cytopathology in the developing world at a full day symposium at the International Academy of Pathology (IAP) Congress in Montreal. At the end of that Congress there was a meeting of more than 60 pathologists from Africa, who had been given bursaries by the US Canadian Division of the IAP to attend the Congress, and other interested pathologists, to discuss what could be done immediately to assist our colleagues in these developing countries. I was invited to provide a FNAB tutorial at Mulago Hospital in Kampala, Uganda by Dr Michael Odida, one of the pathologists at the Makerere University Medical School. Mulago Hospital, where Burkitt of Burkitt's lymphoma fame had worked, is the largest hospital and the only referral hospital in Uganda, a nation of more than 30 million people.

I invited Dr William Geddie from the University Health Network in Toronto, Canada to join me on the faculty. Bill Geddie and I had met at a two week tutorial on performing and interpreting FNAB, at the Karolinska Hospital in 1989, run by one of the founders of FNAB cytology, Dr Torsten Lowhagen. We modelled our planned tutorial on the way in which we have been taught by Torsten Lowhagen and on similar tutorials that we have taught at in Australia and Canada.

In January 2007 we presented a four day, 32 hour tutorial at Mulago Hospital **(Figure 1).** The tutorial focussed on practical sessions on how to perform a FNAB effectively to obtain optimal material, how to smear the material on the slides so as to maximise their diagnostic potential and then how to use a diagnostic approach to interpret the slides.

Bill and I demonstrated how to perform FNABs, initially in a crowded treatment room on the Head and Neck ward and then in Thyroid and Breast outpatient clinics. My first FNAB was on a 14 year old boy, who had been sitting in a ward for two weeks during which time he had had an unsuccessful FNAB and incisional biopsy of a large grapefruit sized neck mass. My FNAB showed a classic Hodgkin's Lymphoma and not the clinically expected Burkitt's lymphoma, and the boy has been subsequently treated successfully in the small Oncology centre at the hospital.

These practical sessions, which demonstrated how FNAB could be performed in an outpatients setting and provide an immediate provisional report of the air dried Giemsa stained smears "at the bedside", really showed to the gathered pathologists and surgeons what could be achieved with the FNAB in their clinical practice.

This galvanised the audience during the following two days of lectures. They could see what a powerful tool FNAB is for triaging patients and, in most cases, providing a definitive diagnosis. The

Figure 1: *Dr Bill Geddie, second from left in front row, and Dr Andrew Field, fifth from left, back row, with the registrants, in front of Mulago Hospital, Kampala, Uganda, January 2007*

huge backlog of patients in the packed wards waiting to have incisional biopsies in the overloaded operating theatres and the large numbers of new patients presenting daily to outpatients could be triaged, diagnosed and in many cases treatment could be commenced or the patient could be sent home for palliative care. For example, FNAB of cervical lymphadenopathy patients can triage them as having tuberculosis, AIDS related lymphadenopathy, lymphoma or metastatic carcinoma **(Figure 2a)**. This relieves the burden of hospitalized patients on the hospital system as these patients do not require hospitalization for clinical assessment and surgical biopsy.

The positive response to the tutorial from the 18 registrants was overwhelming. It obviously takes more than a week long tutorial to train a cytopathologist but the practical tutorial empowers pathologists to perform FNAB, build up their experience and eventually teach. To support them in their development, the St Vincent's Hospital Pathology Service, Sydpath, has paid for couriering slides to St Vincents, where I have reported the cases, emailing these opinions to the Ugandan pathologists, who are charged with making the final diagnosis. Lately, I have received emailed digital microscopic images and emailed back my opinions on these cases to the pathologists.

One of the registrants at the Kampala tutorial, Dr Francis Faduyile, spent five months in 2007 in our St Vincent's Department of Anatomical Pathology studying cytopathology. Recently he sent us images of the FNAB of a large orange sized lesion in the cheek of a five year old boy, which had destroyed his right maxilla, caused massive proptosis of his right eye and derangement of his teeth. A diagnosis of cementifying fibroma was made. This is a locally destructive but non-metastasizing lesion, and at this stage we are hopeful that the boy will be treated in London by a leading maxillofacial surgeon we have contacted.

Subsequently Bill Geddie and I provided a five day tutorial in October 2007 at the Lagos University Teaching Hospital in Lagos, Nigeria where we had 38 registrants including three pathologists from Ghana and trainee and experienced pathologists from all over Nigeria. This tutorial was memorable for the intense interest shown by the registrants in the FNAB technique, their enthusiasm and their demonstrated dedication to their health system which is extremely under resourced and stretched to the limits. Many pathologists and other medical practitioners seek a future outside Nigeria but those that remain are strongly committed to their hospitals and their country while working in very poorly equipped laboratories. During our five days of lectures the electricity failed on many occasions. The extremely noisy backup generator was right outside the lecture theatre. These interruptions have a serious impact on running modern laboratory equipment and even internet access. Again the practical demonstrations of the efficacy and accuracy of FNAB in an outpatient setting had a profound effect on the registrants **(Figure 2b)**. We also presented a lecture on the clinical role of FNAB to the Lagos Medical Society to an audience of 400 doctors and nurses and two TV camera crews.

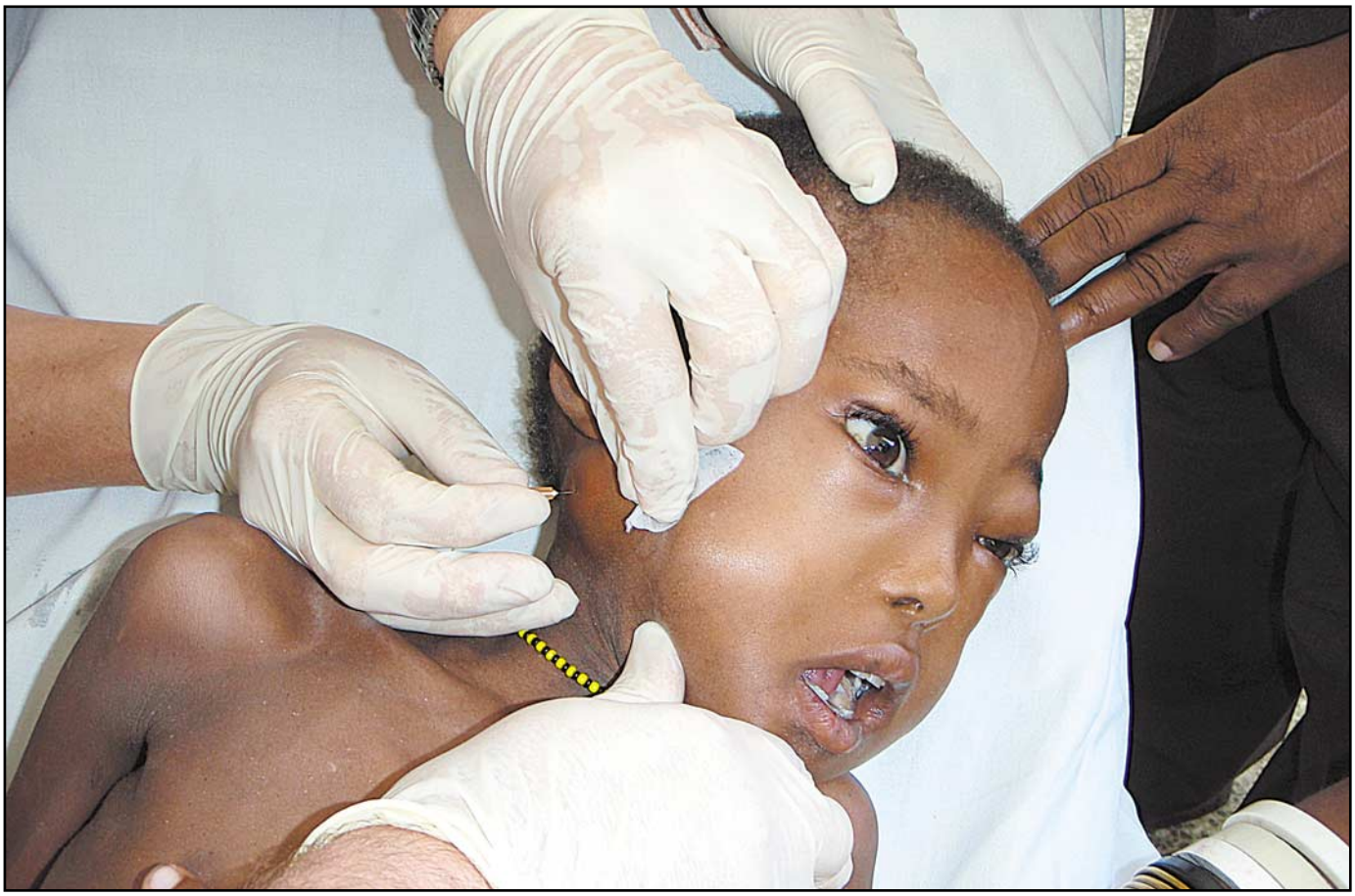

Figure 2(a): *Dr Andrew Field performing a FNAB on a seven year old Masai girl with right cervical lymphadenopathy, with the simple needle technique, at Muhimbili University Teaching Hospital in Dar Es Salaam, January 08.*

In January 2008 a third tutorial was held at Muhimbili University of Health and Allied Sciences in Dar Es Salaam, Tanzania where we had 32 registrants including 16 of Tanzania's 18 surgical pathologists along with three pathologists from Uganda and a number of senior surgeons who were very keen to take part in the actual fine needle aspirations. Dr Matthew Zarka, Head of Cytopathology at the Mayo Clinic, Scottsdale, Arizona joined me as the faculty. Again the response was excellent.

The tutorials have been run under the auspices of the Papanicolaou Society of Cytology, a US based international society associated with the annual United States and Canadian IAP Division Meeting, but the faculty has been self funded. The local hospitals and pathologists have provided basic lecture and clinical facilities and always a lively tutorial dinner. Sydpath has, for each tutorial, provided me with 25kgs of medical supplies including needles, syringes, slides, coverslips and gloves, enough to fill my Samsonite suitcase. The makers of DiffQuick stain, Lab Aids Pty Ltd, have similarly donated four litres of their product, which helped fill the suitcase and perplexed the occasional customs official.

What are our future plans? Bill Geddie and I will run a FNAB tutorial in Nairobi in October 2008 in the four days prior to the Association of Pathologists of Eastern, Central and Southern Africa biannual scientific meeting in Mombasa in Kenya, and then tutorials in March, 2009 in Kano, Nigeria and Dar Es Salaam, Tanzania, with a further six tutorials planned with the International Academy of Cytology and Papanicolaou Society in 2009 and January 2010.

The aim of the tutorials is to train a large number, a "critical mass", of African pathologists in FNAB, gynaecological and general cytology, so that they can not only practice cytopathology, but also teach cytologists and trainee pathologists. To further this, we have actively supported them in the creation of their own cytology societies which can then organise local programmes for scientists to train as cytologists and resident pathologists to train as cytopathologists, with an examination and accreditation system creating career pathways. A detailed syllabus for training cytologists developed recently by the Australian Society of Cytology has been provided to pathologists in Tanzania.

The pathologists are paid poorly in the public sector and all moonlight in the private sector. Now they can generate income by running FNAB clinics and reporting cervical Pap smears based in laboratories requiring minimal infrastructure, compared to a histopathology laboratory. Cytopathology and histopathology are complementary but histopathology laboratories in these African countries are grossly under resourced in equipment, staff and consumables.

The tutorials have been an opportunity to teach the FNAB technique which is eminently suited to the medical system in under resourced countries because it provides rapid, accurate and inexpensive diagnoses of patients, particularly in the outpatient setting. The pathologists trained at these tutorials will continue to develop their FNAB expertise which will assist their patients and the highly stressed medical systems of their respective African nations.

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Figure 2(b): *Dr Andrew Field performing a FNAB on a woman's right breast, with suspected breast carcinoma using the syringe holder, in an outpatient setting. Note the advanced carcinoma involving the left breast. Lagos University Teaching Hospital, October 07*

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